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

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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.

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

ALK inhibitors (ALKi) have now been used for several years in patients with relapsed ALK-positive ALCL with response rates ranging from 53% to 90%. Most previous trials were based on first generation ALKi crizotinib, which is known to have poor CNS penetration. By contrast, next
generation ALKi which have been developed for lung cancer and brain metastases, have good CNS penetration and could be therefore of great interest to treat 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 ALKi 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 each for CNS relapse/progression are available in table 1, table 2 and supplementary table 1.

One patient only had CNS involvement at diagnosis. Of note, all patients received a diagnostic CSF evaluation as routine staging. CNS-imaging was only performed in case of clinical suspicion. Three patients had leukemic presentation or bone marrow involvement at diagnosis and 6 had no particular clinical risk factor for CNS evolution (table 1). Of note, at frontline, all patients at diagnosis, except for one were at high-risk for relapse or progression with positive MDD and MRD after one course. Five patients experienced disease progression while on frontline therapy. For the 5 others who achieved CR 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 5 and after the second or further relapse in 4. Median age at CNS relapse/progression was 11 years (range: 1.8-19). The median delay between diagnosis and CNS relapse/progression in the 9 patients free of CNS involvement at diagnosis was 9 months (range: 1.6-54). Before the initiation of treatment with next generation ALKi, all patients had received 1 to 3 previous treatment lines and 4 of them previously received crizotinib (supplementary table 1). Interestingly, 9 patients had positive MRD while on the treatment line preceding CNS relapse/progression although 8 were in complete clinical and radiological remission (CR). Of note, 6 patients relapsed on CNS while on treatment, either with vinblastine (n=3) or crizotinib (n=3). At the time of CNS progression/relapse, 4 patients had only CNS involvement and the 6 others also had systemic disease. CNS involvement was restricted to the presence of tumor cells on cytological examination in the CSF in 3 patients and 7 patients had intracranial mass, associated with CSF positivity on cytological examination in 3/5 in whom CSF examination could be performed.

Among the 11 episodes of CNS relapse/progression reported here, the next generation ALKi used was either ceritinib (n=3), lorlatinib (n=3) or alectinib (n=5). The median duration of the treatment with next generation ALKi was 11.3 months (range: 1.2- 27.2). Regarding response to these ALKi, we
reported 10 out of 11 CNS relapse/progression. One progression of disease occurred on ceritinib in patient#5 who finally achieved CR after being switch to high-dose methotrexate followed by alecitinib. 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 CR on alecitinib (patient #9). This progression was not well documented neither on a molecular level (i.e. resistance mutation) nor on a pharmacokinetic level. Alecitinib was stopped and this patient benefited from a CNS directed chemotherapy and finally achieved third CR (CR3). She unfortunately died while in CR3 in the context of invasive mucormycosis infection.

Regarding the 9 patients with prolonged CR, 4 patients were still on ALKi at the date of last visit. The treatment was discontinued for the other 5 patients for various reasons:
- One patient (#8) underwent allogeneic hematopoietic stem cell transplantation after CR
- One patient (#3) stopped ceritinib for grade 3 toxicity and was switched to weekly vinblastine for 3 months and received no further treatment after vinblastine, with a follow-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 CR.
- One patient (#5) definitively stopped the next generation ALKi and received no further therapy, with more than 10 months off treatment at the date of last follow-up considered for the study.

Overall, 9/10 patients were alive in CR at the date of last visit. The median follow-up duration from ALKi initiation in these 9 patients was 24.2 months (11.3-48.1).

Of note, next generation ALKi could be helpful in critically ill patients as clinical improvement occurred very fast i.e. for patient #3 who was in a coma at treatment initiation and regained normal consciousness. Response on imaging was also impressive for the patients with intracranial masses (supplementary figure 1).

Regarding tolerance of next generation ALKi, we reported notable adverse events (AE) ≥ grade 3 in 8 patients, notably weight gain in 3 patients and neuropsychological manifestations in 3 patients. Three patients had gastrointestinal and/or hepatic AE grade 3.

In contrast to the overall population of patients with ALK-positive ALCL, patients with CNS involvement anytime during the course of the disease are known to have a dismal outcome. This was recently confirmed in a report from the European Inter-Group for Childhood Non-Hodgkin Lymphoma, with a three-year overall survival of patients after CNS relapse inferior to 50%, and a
median time to death after CNS relapse of 3.5 months in the 4% of patient experiencing such relapses³.

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 ALKi are now widely used to treat patients with ALCL at relapse⁴⁻⁶. There is no evidence that vinblastine and the antibody-drug conjugate brentuximab vedotin cross the blood-brain barrier¹⁰, and several cases of CNS relapses occurring in ALCL patients treated with vinblastine or brentuximab for a systemic disease have been reported¹¹,¹².

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 ALCL⁴⁻⁶. 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 studies¹³. This might be attributed to poor CNS penetration of crizotinib, with a concentration in CSF almost 400 fold lower than in the serum¹⁴. This lack of ALCL CNS disease control with crizotinib was also depicted in brief report by Ruf and colleague in 2018¹¹. To overcome this pitfall, 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 NSCLC¹⁵.

We report here 11 neuro-meningeal relapses or progressions in 10 patients with ALK-positive ALCL treated with next generation ALK inhibitors. We first want to emphasize that this number is quite high as we reported here 10 patients with CNS relapses in 3 years compared to the previous 25 CNS relapses in nearly 20 years reported in the already mentioned EICNHL report³. 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 MRD positive. Of note, 6 of our patients relapsed on vinblastine or crizotinib. In this cohort of 11 CNS relapses treated with next generation ALKi, a rapid, profound response was observed in all 10 patients. Only one patient experienced secondary progression while on next generation ALKi whereas 9 patients were still alive in CR at the date of last follow-up. Even though this series is small, the response rate and general outcome appears far better than relapsed/refractory ALK-positive ALCL with CNS involvement previously reported in the literature³.

The optimal duration of such treatment has not been assessed yet. Of note, though the majority of the patients achieved durable complete remission, they may not be cured since abrupt relapses have
been reported after the discontinuation of ALK inhibitors, even after several years of treatment \(^6\). In this series, one patient is still in complete remission after having stopped his treatment with ALKi for nearly one 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.

References


Tables:

Table 1: Patients’ initial diagnosis and relapse characteristics

Table 2: Response to next generation ALK inhibitors and patients’ outcome
Table 1: Patients' initial diagnosis and relapse characteristics

<table>
<thead>
<tr>
<th>Patient (age at diagnosis in years)</th>
<th>Initial CNS status</th>
<th>Other clinical risk factors for CNS at diagnosis*</th>
<th>MDD/early MRD status in frontline</th>
<th>Histological pattern (SC/LH component vs common)</th>
<th>Delay from EOT to first CNS relapse (months)</th>
<th>Interval between initial diagnosis and CNS involvement (months)</th>
<th>Number of CNS relapse/progression (type)</th>
<th>Last treatment before CNS relapse</th>
<th>Peripheral blood MRD status on previous treatment line</th>
<th>Type of CNS involvement</th>
<th>Type of CNS relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>Negative</td>
<td>No</td>
<td>positive/positive</td>
<td>Common</td>
<td>0.7</td>
<td>54</td>
<td>3, relapse</td>
<td>vinblastine</td>
<td>positive</td>
<td>systemic and CNS</td>
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<tr>
<td>2</td>
<td>6</td>
<td>Negative</td>
<td>Leukemic presentation (blood circulating cells on cytology)</td>
<td>positive/positive</td>
<td>SC/LH</td>
<td>on therapy</td>
<td>4.9</td>
<td>3, progression</td>
<td>vinblastine</td>
<td>positive</td>
<td>systemic including uncontrolled leukemic form</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>Positive</td>
<td>n.a.</td>
<td>n.d.</td>
<td>Common</td>
<td>on therapy</td>
<td>n.a.</td>
<td>1, progression</td>
<td>Radiotherapy</td>
<td>positive</td>
<td>systemic and CNS</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>Negative</td>
<td>Biopsy of choroid plexus papilloma at treatment initiation</td>
<td>positive/positive</td>
<td>Common</td>
<td>on therapy</td>
<td>4.1</td>
<td>1, relapse</td>
<td>vinblastine</td>
<td>positive</td>
<td>CNS only</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>Negative</td>
<td>No</td>
<td>positive/positive</td>
<td>SC/LH</td>
<td>2.1</td>
<td>10.1</td>
<td>1, relapse</td>
<td>ALCL99</td>
<td>negative at EOT with ALCL99</td>
<td>systemic and CNS</td>
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<tr>
<td>6</td>
<td>1.8</td>
<td>Negative</td>
<td>BM involvement (diagnosed on cytology)</td>
<td>positive/positive</td>
<td>SC/LH</td>
<td>on therapy</td>
<td>1.6</td>
<td>1, relapse</td>
<td>ALCL99</td>
<td>positive</td>
<td>systemic including BM and CNS</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>Negative</td>
<td>No</td>
<td>positive/positive</td>
<td>n.d.</td>
<td>on therapy</td>
<td>9</td>
<td>2, relapse</td>
<td>crizotinib</td>
<td>positive</td>
<td>CNS only</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>Negative</td>
<td>No</td>
<td>positive/positive</td>
<td>n.d.</td>
<td>1.5</td>
<td>5.8</td>
<td>1, relapse</td>
<td>ALCL99</td>
<td>positive at EOT with ALCL99</td>
<td>systemic and CNS</td>
</tr>
<tr>
<td></td>
<td>BM involvement</td>
<td>( \text{positive/positive} )</td>
<td>SC/LH</td>
<td>1.9</td>
<td>15.8</td>
<td>2, relapse</td>
<td>crizotinib</td>
<td>positive</td>
<td>CNS only</td>
<td>CNS mass</td>
<td></td>
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<tr>
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<td>---------</td>
</tr>
<tr>
<td>9</td>
<td>Negative BM involvement (diagnosed on cytology) Severe HLH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Negative No</td>
<td>positive/positive</td>
<td>SC/LH</td>
<td>0.6</td>
<td>14.8</td>
<td>2, relapse</td>
<td>crizotinib</td>
<td>positive</td>
<td>CNS only</td>
<td>Multiple CNS masses + CSF positive</td>
<td></td>
</tr>
</tbody>
</table>

Legend: * ie: leukemia presentation, BM involvement, CNS involvement at diagnosis; ALK: ALK inhibitors; BM: bone marrow; CNS: central nervous system; CSF: cerebrospinal fluid; EOT: end of treatment; LH: lymphohistiocytic component; MDD: minimal disseminated disease; early MRD: early measurement (after one chemotherapy course) of minimal residual disease; n.a.: not applicable; n.d.: not done; SC: small cell component
<table>
<thead>
<tr>
<th>Patient</th>
<th>Name of ALKi</th>
<th>Type of CNS involvement</th>
<th>Best response</th>
<th>Delay to best response (months)</th>
<th>Treatment duration (months)</th>
<th>Next treatment after ALKi</th>
<th>Notable Adverse event</th>
<th>Current outcome and disease status [FU from ALKi initiation, in months]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>lorlatinib</td>
<td>CNS mass</td>
<td>CR</td>
<td>6</td>
<td>7</td>
<td>other investigational treatment in CR for consolidation</td>
<td>Hallucinations, anxiety grade 3</td>
<td>alive in CR [30.2]</td>
</tr>
<tr>
<td>2</td>
<td>alectinib</td>
<td>Multiple CNS masses + CSF positive</td>
<td>CR</td>
<td>1.6</td>
<td>14.5</td>
<td>n.a.</td>
<td>Weight gain grade 3</td>
<td>alive in CR [14.5]</td>
</tr>
<tr>
<td>3</td>
<td>ceritinib</td>
<td>CNS mass</td>
<td>CR</td>
<td>0.5</td>
<td>3</td>
<td>vinblastine 3 months then no further treatment</td>
<td>GI toxicity grade 3</td>
<td>alive in CR [48.1]</td>
</tr>
<tr>
<td>4</td>
<td>lorlatinib</td>
<td>Multiple CNS masses</td>
<td>CR</td>
<td>1</td>
<td>27.2</td>
<td>n.a.</td>
<td>Weight gain grade 3</td>
<td>alive in CR [27.2]</td>
</tr>
<tr>
<td>5</td>
<td>ceritinib</td>
<td>CSF positive</td>
<td>PD</td>
<td>1.2</td>
<td>1.2</td>
<td>n.a.</td>
<td>Hepatic toxicity grade 3</td>
<td>alive in CR</td>
</tr>
<tr>
<td>5 [2nd episode treated with ALKi]</td>
<td>alectinib</td>
<td>CSF positive</td>
<td>CR</td>
<td>n.a.</td>
<td>CR obtained with 2 courses of HD MTX</td>
<td>26</td>
<td>no further treatment</td>
<td>Weight gain grade 3</td>
</tr>
<tr>
<td>6</td>
<td>ceritinib</td>
<td>CSF positive</td>
<td>CR</td>
<td>1.3</td>
<td>16.9</td>
<td>other investigational treatment in CR for consolidation</td>
<td>GI and hepatic toxicity grade 3</td>
<td>alive in CR [40.8]</td>
</tr>
<tr>
<td>7</td>
<td>lorlatinib</td>
<td>CNS mass + CSF positive</td>
<td>CR</td>
<td>1.6</td>
<td>21</td>
<td>n.a.</td>
<td>Irritability and aggression grade 2</td>
<td>alive in CR [21.0]</td>
</tr>
<tr>
<td>8</td>
<td>alectinib</td>
<td>CSF positive</td>
<td>CR</td>
<td>2.5</td>
<td>2.9</td>
<td>allo transplant in CR</td>
<td>none</td>
<td>alive in CR [19.1]</td>
</tr>
<tr>
<td>9</td>
<td>alectinib</td>
<td>CNS mass</td>
<td>CR</td>
<td>1.4</td>
<td>2.5</td>
<td>CNS directed chemotherapy for CNS disease progression</td>
<td>none</td>
<td>Died, in CR3 in context of mucormycosis infection [9.4]</td>
</tr>
<tr>
<td>10</td>
<td>alectinib</td>
<td>Multiple CNS masses + CSF positive</td>
<td>CR</td>
<td>3.6</td>
<td>11.3</td>
<td>n.a.</td>
<td>Acute delirium Grade 3</td>
<td>alive in CR [11.3]</td>
</tr>
</tbody>
</table>

Legend: ALKi: ALK inhibitors; CNS: central nervous system; CR: complete response; CR3: third complete response; CSF: cerebrospinal fluid; n.a.: not applicable; n.d.: not done; PD: progressive disease.
Figures

Figure 1: Swimmer-plot of French pediatric patients treated with next generation ALK inhibitors for CNS relapse/progression of ALK+ ALCL
### Supplementary table 1: Summary of treatment lines received by each patient before initiation of next generation ALK inhibitors

<table>
<thead>
<tr>
<th>Patient</th>
<th>Previous treatment lines</th>
</tr>
</thead>
</table>
| 1       | 1/ALCL99 protocol  
2/ & 3/ Vinblastine 2 years x2 |
| 2       | 1/HR T-ALL protocol  
2/ALCL99 + crizotinib  
3/Vinblastine |
| 3       | 1/ Radiotherapy (54Gy) of the intracranial mass (misdiagnosed as HGG) |
| 4       | 1/ALCL99 protocol prephase followed by vinblastine (2 months)  
2/LMB2001 protocol group C (major toxicity) |
| 5       | 1/ALCL99 protocol with 3 vinblastine injections (for wound dehiscence) between BM1 and AM2 courses |
| 6       | 1/ALCL99 protocol |
| 7       | 1/ALCL99 protocol  
2/crizotinib |
| 8       | 1/ALCL99 protocol |
| 9       | 1/crizotinib (2.9 month due to initial clinical poor status) followed by ALCL99 protocol  
2/ vinblastin (6 injections) then switch to crizotinb (because of still positive MRD) |
| 10      | 1/ALCL99 protocol  
2/vinblastin then switch to crizotinib (because of still positive MRD) |

*Legend: MRD: minimal residual disease*
Supplementary figure 1: Brain magnetic resonance imaging of patient #1 with T1 weighted axial images showing, a. contrast-enhanced paramedian left parietal mass with peripheral edema at diagnosis of CNS relapse; b. a sequelar porencephaly after 6 months on lorlatinib