Prevention of hepatic toxicities associated with anaplastic lymphoma kinase inhibitors in the treatment of non-small-cell lung cancer by administration of ursodeoxycholic acid: the monoinstitutional analyses

Background

- ALK gene rearrangement is a driving mutation underlying the development of NSCLC, and has been identified in 5–6% of NSCLC cases.
- The selection of ALK inhibitors showed therapeutic activity in in patients with non-small-cell lung cancer (NSCLC).
- The common toxicities associated with ALK-TKIs are gastrointestinal toxicities including nausea, vomiting and diarrhea, the severity of these toxicities is mild.
- Physicians pay more attention to the incidence and risk of liver toxicities associated with ALK-TKIs when administrating these drugs.
- There are several areas for the pathogenesis of drug-induced liver toxicities have been recommended, including immune mediated response, mitochondrial dysfunction and variations in host metabolic response.
- Ursodeoxycholic acid is a hydrophilic bile acid with membrane-stabilising, cytoprotective, and immunomodulatory effects on liver cells.
- Ursodeoxycholic acid has been tested in various liver diseases and primary sclerosing cholangitis are two diseases in which ursodeoxycholic acid has been used most extensively.

Objective

- To describe outcomes of ursodeoxycholic acid administration in patients in therapy for advanced NSCLC with ALK inhibitors. Patients treated with ALK inhibitors were divided into two groups: the already treated group with experienced liver toxicity and the de novo group.

Methods

- Study design and patients
  - Retrospective review study
  - Patient inclusion criteria:
    - Age ≥18 years old at diagnosis (initial or recrimal) or pathologically confirmed, unresectable stage IIB/C or IV NSCLC with ALK translocation.
    - Initiation of first-line ALK inhibitor monotherapy for advanced NSCLC from February 2016 - February 2022.
    - Recorded tumour ALK translocation test documented by start of first-line ALK inhibitors.
  - Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2.
  - Liver function was assessed at baseline before treatment and monitored every two weeks during the first two months, then monthly.

Assessments and analyses

- Descriptive analysis of patient characteristics by liver metastases and liver function.
- The patients were divided on two groups: on treatment with ALK inhibitor and with liver toxicity G1 and G2 (group 1), in prophylaxis at the start of treatment with ALK inhibitor (group 2).

Results

- Of 82 eligible patients, 35 were group 1, and 45 were group 2.

Table 1. Baseline characteristics of 82 patients with advanced NSCLC, ALK translocation positive: prescribed first-line ALK inhibitors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 N=35</th>
<th>Group 2 N=45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>72 (69–89)</td>
<td>67 (65–77)</td>
</tr>
<tr>
<td>Current/former smoker</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>NSCLC histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-squamous</td>
<td>60 (28–32)</td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>15 (5–8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (2–3)</td>
<td></td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Liver Function (time=0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>38 (20–56)</td>
<td>40</td>
</tr>
<tr>
<td>ALT (IgL/L)</td>
<td>58 (20–72)</td>
<td>60</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>61 (45–78)</td>
<td>66 (58)</td>
</tr>
<tr>
<td>Bil. Tot (μg/dl)</td>
<td>0.8 (0.6–1.2)</td>
<td>0.6 (1.1)</td>
</tr>
</tbody>
</table>

Clinical outcomes:

- In group 1, 25 patients developed liver toxicity G1-G2 and started ursodeoxycholic acid at dose of 450 mg/day per os.
- In group 2 treatment with ALK inhibitors.
- By the end of follow-up, 6 patients had discontinued first-line ALK inhibitors treatment, including 4 who had died.

Table 2. Study design

Key Eligibility Criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- Known ALK alterations
- ECOG PS 0–2

Analyses

- Descriptive analysis of patient characteristics by liver metastases and liver function.
- The patients were divided on two groups: on treatment with ALK inhibitor and with liver toxicity G1 and G2 (group 1), in prophylaxis at the start of treatment with ALK inhibitor (group 2).

Figure 1. Accumulation of hydrophobic bile acids within the hepatocyte induces cell death of liver cells during cholestasis.

Figure 2. Proposed mechanisms of ursodeoxycholic acid (UDCA) inhibition of apoptosis

Figure 3. Group 1 patients

- 23 patients developed liver toxicity G1-G2 and started ursodeoxycholic acid at dose of 450 mg/day.
- The rate of reduction in liver toxicity from G2 and G1 to G0 was 78%.

Conclusions

- Real-world clinical outcomes with ursodeoxycholic acid therapy for patients with advanced NSCLC has shown excellent efficacy in the management of liver toxicity with ALK inhibitors.
- The effective management of hepatic toxicity made possible to maintain an adequate dosage of ALK inhibitors.
- Further studies are needed to define the etiopathogenic mechanism responsible for hepatic toxicity from ALK inhibitors.