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# Transient Elastography Is Not a Predictor of Hepatotoxicity in Newly Diagnosed Acute Lymphoblastic Leukemia Patients Undergoing Asparaginase-Based Induction Chemotherapy

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## BACKGROUND

Asparaginase-based, pediatric-inspired regimens have improved survival of adolescent and young adults with acute lymphoblastic leukemia (ALL), although hepatotoxicity and metabolic toxicities, more common in adults and in the Hispanic population, often limit treatment. The mechanisms of toxicity are not completely understood, but small preclinical and clinical studies suggest liver steatosis may play a role. Ultrasound transient elastography (TE) is a non-invasive diagnostic test used to assess liver stiffness and steatosis, although its ability to predict asparaginase hepatotoxicity is not known.

## AIM

To prospectively evaluate the presence of liver steatosis and/or fibrosis with TE in ALL or lymphoblastic lymphoma (LL) adults undergoing asparaginase-based chemotherapy, and correlate it with hepatotoxicity.

## METHODS

TE was performed in all ALL or LL adults before initiating asparaginase-based treatment (a modified CALGB 10403). According to recently published guidelines, steatosis was defined as a CAP value ≥ 275 dB/m, and absence of fibrosis as an E value < 5 kPa. These parameters and baseline characteristics were correlated with the development of grade 3 or 4 hepatotoxicity, according to CTCAE version 5.

## RESULTS

Forty-three patients were included, 41 (95.3%) with a B-ALL diagnosis and the remaining with LL. Median age at diagnosis was 31 years (range, 18-49) and 21 (48.8%) were women. Steatosis and absence of fibrosis were found in 14 (32.6%) and 11 (25.6%) patients respectively. Remaining baseline characteristics are shown in *Table 1*.

## RESULTS

Grade 3 or 4 hepatotoxicity developed in 20 (46.5%) patients during induction therapy. Thirty-four proceeded to consolidation therapy, of which 20 (58.8%) developed grade 3 or 4 hepatotoxicity. Neither liver steatosis or absence of fibrosis were associated with hepatotoxicity during treatment. Only a white blood cell (WBC) count ≥ 30 × $10^9$/l was associated with this complication during induction, with no correlation found with the rest of the baseline characteristics (*Table 2*). Median CAP and E values of the whole cohort were 248 dB/m and 5.9 kPa, respectively, and these values did not differ between patients who developed and did not develop hepatotoxicity during induction (234 vs 256 dB/m, *p*=0.165, and 5.9 vs 5.9 kPa, *p*=0.904) or consolidation therapy (244 vs 252 dB/m, *p*=0.727, and 5.9 vs 6.2 kPa, *p*=0.951). Regarding the type of hepatotoxicity, during induction, 13 (30.2%) patients had bilirubin and transaminase elevation each, while in consolidation, 10 (29.4%) and 16 (47%) had bilirubin and transaminase elevation, respectively.

| Baseline characteristics N=43 Median (range) or N (%) | |
|---|---|
| Age, years | 31 (18-49) |
| Female sex | 21 (48.8) |
| Body mass index, kg/m$^2$ | 26.9 (13.8-39.8) |
| Overweight or obesity | 26 (60.5) |
| Absence of fibrosis | 11 (25.6) |
| Steatosis | 14 (32.6) |
| WBC count ≥ 30 × $10^9$/l | 9 (20.9) |

*Table 1. Baseline characteristics. Median and frequencies are shown with ranges and percentages in parentheses.*

| Grade 3 or 4 hepatotoxicity *vs.* no hepatotoxicity N (%) | | |
|---|---|---|
| Variable | Induction | OR (IC 95%), p value |
| Age ≥ 30 years | 11 (55) vs 12 (52.2) | 1.12 (0.34-3.73), p=0.853 |
| Male sex | 10 (50) vs 12 (52.2) | 0.92 (0.28-3.04), p=0.887 |
| Overweight or obesity | 11 (55) vs 15 (65.2) | 0.65 (0.19-2.23), p=0.494 |
| Liver steatosis | 4 (20) vs 10 (43.5) | 0.33 (0.08-1.28), p=0.101 |
| Absence of liver fibrosis | 6 (30) vs 5 (21.7) | 1.54 (0.39-6.12), p=0.536 |
| WBC ≥ 30 × $10^9$/l | 8 (40) vs 1 (4.3) | 14.67 (1.63-131.66), p=0.005 |

| Grade 3 or 4 hepatotoxicity *vs.* no hepatotoxicity N (%) | | |
|---|---|---|
| Variable | Consolidation | OR (IC 95%), p value |
| Age ≥ 30 years | 7 (35) vs 10 (71.4) | 0.22 (0.05-0.95), p=0.037 |
| Male sex | 10 (50) vs 7 (50) | 1 (0.26-3.92), p=1 |
| Overweight or obesity | 12 (60) vs 10 (71.4) | 0.6 (0.14-2.6), p=0.717 |
| Liver steatosis | 5 (25) vs 6 (42.9) | 0.44 (0.1-1.92), p=0.458 |
| Absence of liver fibrosis | 5 (25) vs 4 (28.6) | 0.83 (0.18-3.88), p=1 |
| WBC ≥ 30 × $10^9$/l | 4 (20) vs 2 (14.3) | 1.5 (0.24-9.59), p=1 |

*Table 2. Correlation of baseline characteristics with hepatotoxicity during induction and consolidation therapy.*

## CONCLUSIONS

Grade 3 or 4 hepatotoxicity occurred in nearly half of patients undergoing asparaginase-based induction chemotherapy, but transient elastography values did not correlate with the incidence of this complication. There is an unmet need in understanding the mechanisms and prevention of asparaginase induced hepatotoxicity.

## REFERENCES

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