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Original Article

Efficacy of comprehensive treatment in reducing liver fibrosis progression in patients after chemotherapy

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Abstract

Drug-induced liver injury, particularly from anticancer agents, is frequently observed in clinical practice. Despite this, there is currently no standardized treatment strategy for such damage, which represents one of the most serious complications of polychemotherapy. This study evaluates the effect of comprehensive treatment on liver fibrosis progression in patients after polychemotherapy. To assess the potential of combined treatment strategies for managing post-hepatitis liver fibrosis as a drug-induced complication of cytostatic therapy for breast cancer in patients with overweight or obesity. The study included women aged 35–79 years with liver fibrosis (F1-F2) and varying BMI levels (normal weight, overweight, and grade I obesity). Participants were divided into two groups: Group I received non-pharmacological therapy (NPT), while Group II was treated with pharmacological therapy (ursodeoxycholic acid (UDCA) and vitamin E). Comprehensive clinical, laboratory, and instrumental evaluations were conducted to compare treatment outcomes. The administration of UDCA (15 mg/kg/day) and vitamin E (400 IU/day) reduced clinical symptoms, decreased liver stiffness by 17.9% (via shear wave elastography), and normalized liver fibrosis markers (ALT, AST, and Total Bilirubin levels). The proposed treatment significantly reduced liver echogenicity and slowed fibrosis progression in most patients.

Keywords: drug-induced liver injury, polychemotherapy, liver fibrosis, UDCA (ursodeoxycholic acid), obesity, liver elastography

Introduction

In recent years, increasing attention has been focused on toxic liver injuries, including drug-induced liver injury (DILI). Liver fibrosis remains a significant medical challenge, particularly in patients undergoing polychemotherapy. Despite the prevalence of this condition, there are no standardized therapeutic approaches for managing liver fibrosis in this specific patient group [1, 2]. Polychemotherapy is one of the most commonly utilized cancer treatment modalities worldwide, including in Ukraine. However, the long-term management of patients recovering from polychemotherapy poses unique challenges, particularly concerning the treatment of liver fibrosis. Investigating effective therapeutic strategies for this condition is crucial, as the findings could significantly impact clinical practice and improve patient outcomes [3, 4]. This is particularly relevant for addressing fibrosis progression in patients with varying body mass indices (BMIs), including those with overweight or obesity [5]. The study aimed to assess the potential of comprehensive treatment approaches in managing post-hepatitis liver fibrosis as a drug-induced complication of cytostatic therapy for breast cancer, particularly in patients with overweight and obesity.

Material and methods

This study included women aged 35 to 79 diagnosed with liver fibrosis F1 (n=61) and F2 (n=27). Patients were stratified by body mass index (BMI) into normal weight, overweight, and Grade I obesity and were randomly divided into two groups.

All participants had a history of cytostatic therapy for breast cancer and were treated following modern guidelines, including EASL recommendations [6–12].

In group I, patients received non-pharmacological therapy aimed at modifying lifestyle and dietary habits. Recommendations included caloric reduction (10% below calculated energy requirements based on individual needs):

1. Normal-weight patients consume 2200–2400 kcal/ day; overweight/obese patients consume 1200–1800 kcal/day;
2. Low-carbohydrate diets (free sugars ≤10% of daily caloric intake per WHO guidelines);
3. Eliminating processed foods, trans fats, and saturated fats; preference for monounsaturated fats;
4. Adoption of Mediterranean diet principles and DASH diet for patients with cardiovascular comorbidities;
5. Structured meals: three main meals and one snack with 3–4 hours intervals, and dinner 2–3 hours before sleep;
6. Adequate hydration: minimum 1.5 L/day based on individual anthropometric data.

Physical activity recommendations included 150 minutes of moderate aerobic exercise per week (*e.g.*, brisk walking) and muscle-strengthening exercises twice weekly. For higher-intensity regimens, activities included running and increased resistance training.

In group II, patients followed the same non-pharmacological regimen, with the addition of pharmacological therapy comprising ursodeoxycholic acid (UDCA, 15 mg/kg/day) and vitamin E (400 IU/day) for three months.

Patients were monitored biweekly over two months to adjust treatment protocols as necessary. At the end of the treatment course, evaluations included anthropometric measurements, biochemical analyses, direct and indirect fibrosis markers, ultrasonography, liver elastography, and the FIB-4 index.

Statistical analyses were performed using SPSS Statistics 26.0 and Microsoft Excel. Normality was assessed through exploratory analysis, and comparisons between groups were made using the Student's t-test and paired t-tests for repeated measures. Pearson and Spearman correlation tests were used for continuous and non-parametric variables. Results were considered significant at $p<0.05$.

Results

Thus, after analyzing the clinical symptoms, an improvement in the well-being of the examined patients was noted (Table 1).

Table 1: Clinical symptoms.

Clinical symptoms	Group I (NPT)		Group II (PT)	
	Before treatment	After treatment	Before treatment	After treatment
Asthenovegetative syndrome	28 (22.76%)	16 (13%)	28 (22.76%)	8 (6.5%)
	p<0.01*		p<0.01*	
Dyspeptic syndrome	16 (13%)	11 (8.94%)	16 (13%)	6 (4.87%)
	p<0.01*		p<0.01*	
Heaviness in the right hypochondrium	17 (13.82%)	10 (8.13%)	18 (14.63%)	6 (4.87%)
	p<0.01*		p<0.01*	
Hepatomegaly	31 (25.2%)	21 (17.07%)	32 (26.02%)	10 (8.13%)
	p<0.01*		p<0.01*	
AP	15 (12.20%)	11 (8.94%)	16 (13%)	9 (7.32%)
	p=0.01*		p<0.01*	

Note: The significance of the difference between Group I and Group II according to the Wilcoxon criterion is $p<0.05$.

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Analyzing the dynamics of clinical syndromes using the non-parametric Wilcoxon signed-rank test shows that under the influence of treatment, the manifestations of syndromes such as asthenovegetative, dyspeptic, and the feeling of heaviness in the right hypochondrium decreased in both groups. Significant changes were present in the group of patients receiving PT, while patients receiving NPT showed minor changes ($p<0.05$). In turn, the asthenovegetative syndrome remained in half of the examined patients – 13% from 22.76%, dyspeptic in 8.94% from 13% of the total share of patients, and the feeling of heaviness in the right hypochondrium remained in 10 out of 17 patients. Liver enlargement was present in 17% of the examined patients from 25%, while an increase in blood pressure was observed in 8.94% from 12.20%. Patients receiving comprehensive drug therapy showed positive dynamics in two-thirds of the examined patients, indicating its effectiveness compared to lifestyle modification (Figure 1).

After analyzing the clinical indicators using a similar algorithm with the non-parametric Wilcoxon criterion, the dynamics of anthropometric data were evaluated after the course of PT and NPT in the respective patient groups. Thus, the results obtained indicate the different effectiveness of the PT and NPT methods with some differences (Table 2).

The results showed a decrease in all anthropometric indicators, including BMI values, in both groups receiving MT and NMT. However, it is noteworthy that patients who received UDCA and vitamin E in appropriate doses, in addition to lifestyle modification, showed more significant results.

The analysis of the dynamics of biochemical indicators showed more significant changes compared to the dynamics of anthropometric changes, as the examinations before treatment were conducted during the period between cycles of polychemotherapy to confirm the toxic effect of the latter on the state of liver metabolism one month after the treatment and three months later, respectively. Thus, the patients receiving PT and NPT groups demonstrated the following changes (Tables 3 and 4). It is noticeable that under the influence of detoxification therapy during the cycle of polychemotherapy, the dynamics of the main biochemical indicators slightly improved while the activity of the process remained. Thus, patients who received four weeks of medication treatment showed slight positive dynamics. Total bilirubin and albumin levels did not change significantly and remained within normal reference values, with a slight significant increase in the latter ($p<0.05$). A similar trend was observed in the analysis of the dynamics of GGT levels. However, it is worth noting that the final normalization of its values did not occur in all patients (minimum level at 11 U/L, maximum – 76 U/L, respectively, $p<0.05$). The levels of ALT and AST transaminases slightly decreased under

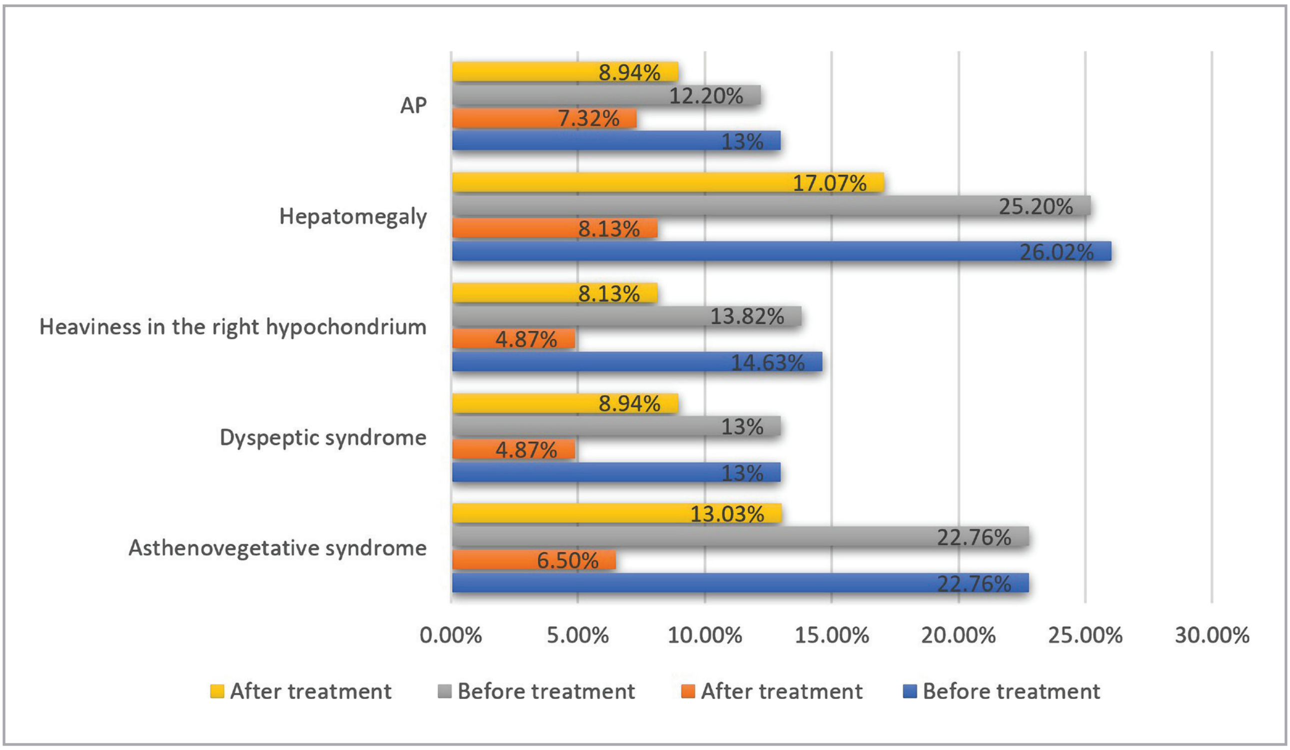

Figure 1: Dynamics of clinical indicators in patients with different body weights after therapy.

Table 2: Dynamics of anthropometric indicators.

Indicators	Group I		Group II	
	Before treatment	After treatment	Before treatment	After treatment
Waist circumference, cm	108.21±1.84	95.65±2.14	87.11±5.79	82.59±5.58
	p<0.01*		p<0.01*	
Hip circumference, cm	112.16±1.90	106.6±1.97	103.18±4.50	96.75±3.97
	p<0.01*		p<0.01*	
Waist-to-hip ratio	0.86±0.02	0.84±0.01	0.91±0.04	0.87±0.03
	p<0.01*		p<0.01*	
Body weight, kg	74.70±9.84	71.70±9.01	72.59±7.67	68.98±6.25
	p<0.01*		p<0.01*	
BMI	26.95±3.55	25.95±3.17	25.93±2.28	24.56±1.74
	p<0.01*		p<0.01*	

Note: The significance of the difference between Group I and Group II according to the Wilcoxon criterion is p<0.05

the influence of PT but still indicated minimal activity of the process (p<0.05).

In contrast to the representatives of this group, patients receiving NPT did not show positive dynamics among the studied indicators (Table 4). Moreover, there was a slight increase in ALT and AST levels (p<0.05), proving the insufficient effectiveness of NPT and requiring a modified approach to treating this condition. The albumin content did not change significantly, and a similar trend was observed in the analysis of total bilirubin dynamics (p<0.05).

After this, patients in both groups continued NPT and PT for another two months. Thus, after completing the course of modified therapy, Group II showed significant positive dynamics in the normalization of AST and ALT activity indicators, which decreased by 1.17 and 1.11 times, respectively, compared to the results after the first month of treatment (p<0.05). The levels of biochemical indicators, such as total bilirubin, GGT, and albumin, were within normal reference values.

The analysis of the main biochemical indicators of Group I patients showed a similar picture in the data

Table 3: Dynamics of the main biochemical indicators in patients receiving pharmacological therapy.

Biochemical indicators	During chemotherapy	One month after the end of chemotherapy	One month after treatment	Three months after treatment
Total Bilirubin (μmol/L)	26.98±7.34	11.44±4.64	10.85±4.44	10.54±3.97
	p<0.01*		p<0.01*	
ALT (U/L)	44.93±19.11	36.26±15.52	35.40±8.33	31.91±6.69
	p<0.01*		p<0.01*	
AST (U/L)	72.05±35.75	39.94±13.86	36.48±9.77	31.06±6.60
	p<0.01*		p<0.01*	
GGT (U/L)	92.69±37.74	30.61±15.42	28.53±14.10	27.06±9.42
	p<0.01*		p<0.01*	
Albumin (g/L)	26.66±8.42	40.95±4.86	43.09±4.42	47.11±4.14
	p<0.01*		p<0.01*	

Note: The significance of the difference according to the Wilcoxon criterion: * – p<0.05.

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Table 4: Dynamics of the main biochemical indicators in patients receiving non-medication therapy.

Biochemical indicators	During chemotherapy	One month after the end of chemotherapy	One month after treatment	Three months after treatment
Total Bilirubin (µmol/L)	33.39±8.14	12.87±5.53	12.81±5.08	12.99±6.48
	p<0.01*		p<0.01*	
ALT (U/L)	65.55±22.34	36.26±15.52	36.89±11.67	35.30±11.07
	p<0.01*		p<0.01*	
AST (U/L)	111.05±42.27	45.02±15.76	42.93±14.64	41.91±13.52
	p<0.01*		p<0.01*	
GGT (U/L)	136.03±41.91	33.23±21.39	32.2±20.43	30.88±19.80
	p<0.01*		p<0.01*	
Albumin (g/L)	20.52±5.7	41.25±5.23	43.43±5.02	46.77±4.39
	p<0.01*		p<0.01*	

Note: The significance of the difference according to the Wilcoxon criterion: * – p<0.05.

of total bilirubin, GGT, and albumin (Table 4). However, the analysis of transaminase activity dynamics revealed the following: AST and ALT levels remained elevated up to three times the norm for AST, with a maximum mark of 73.5 U/L and up to two times the norm for ALT, with a maximum mark of 59.0 U/L, respectively.

Additionally, a correlation analysis was conducted to identify the relationship between changes in BMI values in patients and the positive dynamics of transaminase levels. Thus, a significant correlation was established between the increase in ALT levels and the increase in BMI (p<0.05, r=0.36), WC (p<0.05, r=0.46), and WHR (p<0.05, r=0.36), and AST levels with BMI (p<0.05, r=0.39), WC (p<0.05, r=0.49), and WHR (p<0.05, r=0.39).

Given the observed dynamics after treatment, patients underwent a repeated study of liver elastographic density. Thus, under the influence of treatment, the latter showed significantly better results after 3 months for Group II patients and no significant changes for Group I patients (Table 5). Additionally, a direct correlation was found between decreased liver elastographic density indicators and BMI (p<0.05, r=0.77).

Discussion

This study demonstrated that a comprehensive treatment approach combining pharmacological therapy (UDCA and vitamin E) with non-pharmacological lifestyle modifications significantly improved clinical, biochemical, and elastographic indicators of liver fibrosis in patients following cytostatic therapy for breast cancer. Patients in Group II showed a greater reduction in liver stiffness and more pronounced normalization of liver function markers compared to those who received only lifestyle interventions (Group I), emphasizing the therapeutic potential of combined interventions.

The reduction in AST and ALT levels in Group II aligns with existing studies that underscore the hepatoprotective role of UDCA and antioxidants in drug-induced liver injury (DILI) [6, 8]. Moreover, the use of

Table 5: Indicators of liver elastographic density in the dynamics of observation.

Indicator	Group I		Group II	
	Before treatment	After treatment	Before treatment	After treatment
Liver elastographic density, kPa	7.29±0.01	6.95±0.74	6.56±0.91	5.38±0.63
	p<0.01*		p<0.01*	

Note: The significance of the difference according to the Wilcoxon criterion: * – p<0.05.

vitamin E in patients with metabolic disorders has been associated with improved liver histology, as shown in studies on non-alcoholic steatohepatitis (NASH) and liver fibrosis [5, 9]. Our findings also support recommendations outlined in the EASL Clinical Practice Guidelines for chronic liver diseases, which advocate for nutritional interventions and antioxidant supplementation [7, 10].

A key strength of our study is its focus on patients with varying BMI categories, a critical factor considering the well-documented association between obesity and fibrosis progression [5, 11]. The correlation between elevated BMI and persistent transaminase activity reinforces the need for targeted strategies in overweight populations.

However, several limitations should be acknowledged. First, the relatively short follow-up period (three months) may not fully capture fibrosis's long-term progression or regression. Second, the study relied on non-invasive assessments (elastography and serum biomarkers) without histological confirmation via liver biopsy, which remains the gold standard. Third, the patient population consisted solely of women, which may limit the generalizability of the findings.

Despite these limitations, the study provides important insights into the potential of combined therapy in mitigating liver fibrosis progression after chemotherapy. The results indicate that pharmacological support enhances the effects of lifestyle modification and may be particularly beneficial for patients with increased liver stiffness or metabolic risk factors.

Future research should evaluate the long-term effects of such interventions, include a broader patient demographic, and consider histological verification of fibrosis changes. Additionally, investigating the molecular mechanisms underlying the observed therapeutic benefits may further validate the clinical application of these findings.

This study supports the integration of UDCA and vitamin E into post-chemotherapy care for patients with DILI and early-stage liver fibrosis. The combined approach offers a promising strategy for attenuating fibrosis progression, improving liver function, and enhancing overall patient outcomes.

Conclusions

Lifestyle modification, including diet, water intake, and exercise regimen according to EASL recommendations (EASL Clinical Practice Guidelines: Drug-induced liver injury; Nutrition in Chronic Liver Disease) in Group I patients led to a slight improvement in the clinical picture and laboratory test results but did not achieve results that could indicate fibrosis regression. Based on a thorough analysis of the dynamics of clinical manifestations, blood enzyme spectrum indicators, and instrumental examination indicators, it was found that the additional administration of UDCA at a dose of 15 mg/kg per day and vitamin E at a dose of 400 IU per day during the same period contributed to a reduction in clinical manifestations of the disease and liver parenchyma stiffness indicators according to shear wave elastography (by 17.9%) in Group II patients. According to dynamic observation, the inclusion of these drugs in the treatment regimen contributed to the normalization of indirect liver fibrosis indicators such as ALT and AST, as well as total cholesterol levels. Therefore, the proposed method of treatment optimization in a significant portion of patients allows not only to reduce the degree of liver echogenicity but also to slow down the rate of liver fibrosis. Thus, the proposed method of treatment optimization in a significant portion of patients allows not only to improve laboratory indicators of liver function but also to reduce the severity of liver fibrosis.

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Conflict of interest

The authors declare no conflict of interest.

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