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ORIGINAL RESEARCH

The Safety and Efficacy of Anticancer Therapy in Breast Cancer Patients with Liver Cirrhosis

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Purpose: Special populations are not enrolled in randomized clinical trials, and their safety and efficacy of anticancer therapy are not well described. We aimed to assess the safety and efficacy of anticancer therapy in breast cancer (BC) patients with cirrhosis.

Patients and methods: We performed a retrospective case-control study (1:5) to assess the adverse events (AEs) morbidity and mortality of anticancer therapy in BC patients with cirrhosis based on a review of patients' medical records.

Results: We included 26 BC patients with cirrhosis and 130 matched BC patients without cirrhosis. Postoperative morbidity was higher in the group with cirrhosis (26.9% vs 6.9%, P = 0.007) when postoperative mortality was not significance (3.8% vs 0%, P = 0.167). Liver toxicity (73.1% vs 26.9%, P < 0.001) was more frequent in the group with cirrhosis. The incidence of disruption and mortality during chemotherapy was higher in the group with cirrhosis (46.2% vs 3.1%, P < 0.001 and 15.4% vs 0%, P = 0.001, respectively). The 2-year recurrence rate and 2-year metastasis rate were higher in the group with cirrhosis (19.0% vs 3.8%, P = 0.022 and 23.8% vs 6.9%, P = 0.028). Cirrhosis was the risk factor for liver metastasis (OR: 17.326, 95% CI: 2.164–138.707, P=0.007).

Conclusion: It is safe for BC patients with compensated cirrhosis to accept surgery. But they are vulnerable to AEs, disruptions and death during chemotherapy and have poor prognosis. Multidisciplinary cooperation before therapy and closely monitoring AEs during therapy are critical. Attention should be given to optimize the prognosis of special BC patients.

Keywords: breast cancer, liver cirrhosis, anticancer therapy, safety, efficacy

Introduction

Breast cancer (BC) is the most prevalent cancer and the dominant cause of cancer death among women all over the world, accounting for an estimated 25% of all cancer diagnoses and 15% of all cancer deaths.[1] Though the mortality has declined because of medical advances, the morbidity and mortality of BC remain high,[2] and BC is an enormous disease burden on global society. Though early detection and advances in treatment improved the prognosis of BC patients, there are still some special patient populations for whom treatment can be difficult as clinical studies usually exclude patients with underlying diseases.

The prevalence of liver cirrhosis (LC) is increasing worldwide because of the high prevalence of chronic hepatitis B and hepatitis C, alcoholic liver diseases, as well as the epidemic of non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD).[3,4] Additionally, cirrhosis was the 12th leading cause of mortality all over the world responsible for about one million deaths;[5] it is a great burden on public health care. Moreover, liver cirrhosis is a well-known risk factor for developing extrahepatic cancers.[6] Cancer and liver cirrhosis have common risk factors such as alcohol abuse, tobacco, and the metabolic syndrome. Given that a great number of patients with cancer may concomitantly suffer from liver cirrhosis.[6]

LC can be a risk factor for surgery, due to the pathophysiology of liver disease and the existence of contributing factors, such as adaptive immune dysfunction, poor nutritional status, coagulopathy, renal and pulmonary dysfunction, as well as cirrhotic cardiomyopathy.[7–9] Moreover, liver dysfunction may lead to disruption of chemotherapy so as to reduce

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the effectiveness or cause treatment failure.[10–12] The diminished liver function in patients with LC may alter hepatic drug metabolism, which can lead to higher or more persistent drug levels, causing increased systemic toxicity (especially myelosuppression) or liver function deteriorated from chemotherapy-associated hepatotoxicity.[13] The existence of LC may increase the risk of adverse events (AEs) and increase the physical, psychological, and financial burden of the patient and society.

Although the therapeutic advances have improved the overall prognosis of BC patients greatly, there is little data available on anticancer therapy related safety and efficacy in BC patients with LC. This can be an unintended consequence of the strict enrollment criteria for randomized clinical trials, which often result in the exclusion of special populations. The safety and efficacy of anticancer therapy in BC patients with LC are therefore not well described and may even be underreported. Better understanding of the anticancer therapy related safety and efficacy may lead to improved prevention and prognosis, and can help clinicians select the optimal treatment option for BC patients with LC. Therefore, the present study aimed to evaluate the safety and efficacy of anticancer therapy in BC patients with LC.

Methods

We performed a hospital-based case-control study (1:5) at the Third Affiliated Hospital of Sun Yat-sen University, the Liuzhou Women and Children's Medical Center and the Guangzhou Women and Children's Medical Center between January 2013 and December 2022 to determine the anticancer therapy-related morbidity and mortality in BC patients with LC. Twenty-six BC patients with LC and 130 controls were enrolled in this study. The cases were LC patients newly diagnosed with breast cancer by pathologists. Liver cirrhosis is defined as the development of fibrosis and regenerative nodules in response to chronic liver injury, which results in portal hypertension and end-stage disease. The diagnosis of liver cirrhosis was made by clinical presentation, physical examination, laboratory findings such as liver transaminases or imaging examinations (ultrasonography, CT, or MRI).[14] The controls were diagnosed with breast cancer by pathologists and did not have liver disease. Cases and controls were matched (1:5) by gender, age (± 5 years), tumor histology stage, surgical procedure, and type of chemotherapy. Patients' characteristics, including gender, age, tumor histology, human epidermal growth factor receptor 2 (HER-2)/neu status (according to fluorescent in situ hybridization and/or immunohistochemistry), hormone receptor status (progesterone receptor and/or estrogen receptor), blood cell count (white blood cell (WBC), neutrophil (NEUT), lymphocyte (LYM), platelet (PLT), and hemoglobin (Hb)), liver function (aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), albumin (ALB), and prothrombin time (PT)), renal function (creatinine), Child-Pugh class, surgical procedure, type of chemotherapy anthracycline (doxorubicin) based therapy, taxane (docetaxel) based therapy, anthracycline (doxorubicin) + taxane (docetaxel) based therapy, endocrine therapy (letrozole) only, and other therapy (everolimus or carboplatin + vinorelbine), the morbidity of AEs, mortality, 2-year recurrence and 2-year metastasis, were retrospectively investigated based on a review of patients' medical records.

The study was approved by the ethics committee of the Third Affiliated Hospital of Sun Yat-sen University [Approval No. II2024-214-01]. All volunteers agreed to participate in this study by giving written informed consent. The study was performed in accordance with the guidelines set forth by the Declaration of Helsinki.

Assessment of Adverse Events

Data regarding AEs were evaluated by Common Terminology Criteria for Adverse Events version 5.0.

Statistical Analyses

We used IBM SPSS version 19.0 (IBM, Armonk, NY, USA) to conduct statistical analyses. The baseline demographic and clinical characteristics were listed as mean values with standard deviation or percentages. Propensity-score matching (PSM) was performed to match the two groups. The matching algorithm was based on logistic regression and included gender, age (± 5 years), tumor histology stage, surgical procedure, and type of chemotherapy. A penalty was added when propensity scores differed by more than 0.1× the standard deviation. Nearest-neighbor matching was used. The χ^2 test (Fisher's exact test) was used to evaluate categorical variables and the *t*-test or Mann–Whitney *U*-test was used to

evaluate numerical variables; multivariate logistic regression analysis was used to determine the risk factors associated with 2-year recurrence rate and 2-year metastasis rate; differences were defined as significant when $P < 0.05$.

Results

Baseline Characteristics of the Case and Control Groups

The characteristics of the cases and controls are listed in Table 1. Twenty-six BC patients with LC and 130 matched BC patients without LC were included. No statistical differences were detected in sex, age, tumor histology stage, tumor pathology, surgical procedure, or chemotherapeutic regimens ($P > 0.05$). ALT, AST, TBIL, GGT, and ALP levels were higher in BC patients with LC than in controls. ALB level was lower and PT was longer in BC patients with LC than in controls. Eight (30.8%) BC patients with LC had abnormal blood cell counts, including leukopenia, lymphopenia, anemia and thrombocytopenia; none of patients in the control group had abnormal blood cell counts. Before receiving any treatment, ten (38.5%) BC patients with LC had abnormal liver function; none of patients in the control group had abnormal liver function. Twenty-four BC patients with LC were classified as Child-Pugh A class, and two patients were classified Child-Pugh B class (Table 1). None of patients had liver metastases at diagnosis. The main etiology of LC was chronic hepatitis B (CHB) (61.5%). The therapy of LC was based on the guideline.[3]

Table 1 Baseline Characteristics of the Case and Control Groups

	Control Group	BC Patients with LC	P-value
Total No. of patients	130	26	–
No. of women	130 (100%)	26 (100%)	–
Age (years)	56.2 ± 8.9	58.9 ± 9.0	0.167
ALT (U/L)	15.6 ± 6.9	34.8 ± 20.6	< 0.001
AST (U/L)	19.2 ± 5.2	44.1 ± 27.4	< 0.001
TBIL (μmol/L)	10.2 ±3.9	18.8 ± 10.2	< 0.001
GGT (U/L)	20.9 ± 12.3	56.3 ± 72.9	< 0.001
ALP (U/L)	61.4 ± 17.3	112.6 ± 75.7	< 0.001
ALB (g/L)	42.4 ± 3.7	37.3 ± 3.1	< 0.001
PT (s)	13.0 ±0.7	14.6 ± 1.4	< 0.001
Cr (μmol/L)	56.6 ± 13.1	59.6 ± 10.2	0.195
WBC ($\times 10^9$/L)	6.3 ± 1.9	5.5 ± 1.5	0.042
NEUT ($\times 10^9$/L)	4.1 ± 1.7	3.4 ± 1.1	0.07
LYM ($\times 10^9$/L)	1.8 ± 0.6	1.5 ± 0.5	0.049
Hb (g/L)	123.6 ± 13.9	120.8 ± 12.1	0.352
PLT ($\times 10^9$/L)	256.7 ± 64.4	120.8 ± 12.1	< 0.001
Abnormal blood cell count	0	8 (30.8%)	< 0.001
Abnormal liver function	0	10 (38.5%)	< 0.001

(*Continued*)

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Table 1 (Continued).

	Control Group	BC Patients with LC	P-value
Child-Pugh class			–
A	–	24 (92.3%)	–
B	–	2 (7.7%)	
C	–	0	
Stage			0.144
I	6 (4.6%)	3 (11.5%)	
II	84 (64.6%)	13 (50.0%)	
III	37 (28.5%)	8 (30.8%)	
IV	3 (2.3%)	2 (7.7%)	
Tumor pathology			
Histology			0.742
Invasive ductal carcinoma	113 (86.9%)	24 (92.3%)	
Noninvasive ductal carcinoma	17 (13.1%)	2 (7.7%)	
Immunohistochemistry			
ER status			0.800
Negative	30 (23.1%)	5 (19.2%)	
Positive	100 (76.9%)	21 (80.8%)	
PR status			0.639
Negative	37 (28.5%)	6 (23.1%)	
Positive	93 (71.5%)	20 (76.9%)	
HER-2 status			0.309
Negative	114 (87.7%)	25 (96.2%)	
Positive	16 (12.3%)	1 (3.8%)	
Chemotherapeutic regimen(s)			0.105
Anthracycline-based	8 (6.2%)	2 (7.7%)	
Taxane-based	5 (3.8%)	3 (11.5%)	
Anthracycline- + Taxane-based	108 (83.1%)	17 (65.4%)	
Endocrine therapy only	6 (4.6%)	2 (7.7%)	
Others	3 (2.3%)	2 (7.7%)	
Targeted therapy (Trastuzumab therapy)	16 (12.3%)	1 (3.8%)	0.309

Abbreviations: BC, breast cancer; LC, liver cirrhosis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; ALB, albumin; PT, prothrombin time; Cr, creatinine; WBC, white blood cell; NEUT, neutrophil; LYM, lymphocyte; Hb, hemoglobin; PLT, platelet; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

Morbidity and Mortality of the Two Groups After Surgery

Both groups mainly underwent modified radical mastectomy (93.1% and 88.5% respectively). One stage IV BC patient with LC did not undergo surgery. Seven (26.9%) BC patients with LC and nine (6.9%) control patients had complications after surgery. One (3.8%) BC patient with LC died after surgery due to liver failure (Table 2). Postoperative morbidity was significantly higher in BC patients with LC than in controls (26.9% vs 6.9%, P = 0.007). There was no significant difference in postoperative mortality between the two groups (3.8% vs 0%, P = 0.167) (Table 2).

Morbidity and Mortality of the Two Groups During Chemotherapy

Nineteen (73.1%) BC patients with LC exhibited liver toxicity, including three (11.5%) patients with grade 1, three (11.5%) patients with grade 2, five (19.3%) patients with grade 3, four (15.4%) patients with grade 4 and four (15.4%) patients with grade 5 toxicity. Four (15.4%) BC patients with HBV-related LC died following chemotherapy due to liver failure (grade 5 toxicity) (Table 3).

Table 2 Morbidity and Mortality of Surgery for Breast Cancer in Patients with and without Liver Cirrhosis

	Control Group	BC Patients with LC	P value
Surgical procedure			0.132
Modified radical mastectomy	121 (93.1%)	23 (88.5%)	
Mastectomy	9 (6.9%)	2 (7.7%)	
No applied	0	1 (3.8%)	
Occurrence of complication	9 (6.9%)	7 (26.9%)	0.007
Subcutaneous hydrops	4 (3.1%)	3 (11.5%)	
Lymphedema	3 (2.3%)	2 (7.7%)	
Fever	2 (1.5%)	1 (3.8%)	
Liver failure	0	1 (3.8%)	
Occurrence of death	0	1 (3.8%)	0.167

Abbreviations: BC, breast cancer; LC, liver cirrhosis.

Table 3 Morbidity and Mortality of Chemotherapy for Breast Cancer in Patients with Liver Cirrhosis

	Control Group	BC Patients with LC	P value
Occurrence of liver toxicity			
Total No. of patients	35 (26.9%)	19 (73.1%)	< 0.001
Grade 1	28 (21.5%)	3 (11.5%)	
Grade 2	4 (3.1%)	3 (11.5%)	
Grade 3	2 (1.5%)	5 (19.3%)	
Grade 4	1 (0.8%)	4 (15.4%)	
Grade 5	0	4 (15.4%)	

(*Continued*)

Table 3 (Continued).

	Control Group	BC Patients with LC	P value
Occurrence of myelosuppression			
Total No. of patients	92 (70.8%)	22 (84.6%)	0.225
Grade 1	20 (15.4%)	4 (15.4%)	
Grade 2	26 (20.0%)	11 (42.3%)	
Grade 3	21 (16.2%)	3 (11.5%)	
Grade 4	25 (19.2%)	4 (15.4%)	
Other adverse events			
Total No. of patients	0	4 (15.4%)	0.001
Renal injury	0	1 (3.8%)	
Gastrointestinal bleeding	0	1 (3.8%)	
Infection	0	1 (3.8%)	
Ascites	0	1 (3.8%)	
Disruption in chemotherapy	4 (3.1%)	12 (46.2%)	< 0.001
Death in chemotherapy	0	4 (15.4%)	0.001

Abbreviations: BC, breast cancer; LC, liver cirrhosis.

Thirty-five (26.9%) patients in the control group exhibited liver toxicity, including twenty-eight (21.5%) with grade 1, four (3.1%) patients with grade 2, two (1.5%) patients with grade 3, and one (0.8%) with grade 4 toxicity. The incidence of liver toxicity was significantly higher in the cirrhosis group compared to the control group (73.1% vs 26.9%, $P < 0.001$), particularly grade 3, 4 and 5 toxicity (50.1% vs 2.3%, $P < 0.001$).

Twenty-two (84.6%) BC patients with LC exhibited myelosuppression, including four (15.4%) with grade 1, eleven (42.3%) with grade 2, three (11.5%) with grade 3, and four (15.4%) with grade 4 myelosuppression. Ninety-two (70.8%) patients in the control group presented with myelosuppression, including twenty (15.4%) with grade 1, twenty-six (20.0%) with grade 2, twenty-one (16.2%) with grade 3, and twenty-five (19.2%) with grade 4 myelosuppression. The incidence of myelosuppression was higher in patients with LC, although the difference was not statistically significant (84.6% vs 70.8%, $P = 0.225$).

In addition, among the BC patients with LC, one patient exhibited renal injury (grade 2), one patient exhibited gastrointestinal bleeding (grade 3), one patient exhibited ascites (grade 3), and one patient exhibited infection (grade 2) during chemotherapy. The incidence of other AEs was higher in the cirrhosis group (15.4% vs 0%, $P = 0.001$). The incidence of severe AEs of other organ systems (grade 3) was also significantly higher in BC patients with LC (7.7% vs 0%, $P = 0.027$).

Twelve (46.2%) BC patients with LC experienced disruptions in chemotherapy, including ten (38.5%) patients with chemotherapy termination and two (7.7%) with dose delayed attributable to AEs. Nine patients had disruptions in chemotherapy due to liver toxicity and three patients had disruptions in chemotherapy due to myelosuppression. Among them, nine patients anthracycline received (doxorubicin) + taxane (docetaxel)- based therapy, one patient received anthracycline (doxorubicin)- based therapy, and two patients received other therapy (everolimus or carboplatin + vinorelbine). Four (3.1%) patients in the control group had disruptions in chemotherapy attributable to AEs with dose delayed. Among them, two patients experienced disruptions in chemotherapy due to liver toxicity and two patients experienced disruptions in chemotherapy due to myelosuppression. Two patients received anthracycline (doxorubicin) + taxane (docetaxel)- based therapy, one

patient received anthracycline (doxorubicin)- based therapy, and one patient received other therapy (carboplatin + vinorelbine). The main cause of the disruptions in chemotherapy was liver toxicity in BC patients with LC. No statistical difference was detected in the incidence of disruptions in chemotherapy among the different chemotherapeutic regimens in both groups (P = 0.411 in BC patients with LC when P = 0.059 in control group). The incidence of chemotherapy disruptions attributable to AEs was significantly higher in the LC group compared to the control group (46.2% vs 3.1%, P < 0.001) (Table 3).

Four BC patients with LC died during chemotherapy due to liver toxicity. Among them, two patients received anthracycline (doxorubicin) + taxane (docetaxel) - based therapy, one patient received anthracycline (doxorubicin)-based therapy, and one patient was treated with other therapy (everolimus). No statistical difference was detected in the mortality of chemotherapy among different chemotherapeutic regimens in BC patients with LC (P = 0.268). Liver toxicity was the primary cause of chemotherapy-related mortality (4/4, 100%). The mortality of chemotherapy attributable to AEs was significantly higher in the LC group compared to the control group (15.4% vs 0%, P = 0.001) (Table 3).

Mortality Related to Surgery and Chemotherapy, 2-Year Recurrence and 2-Metastasis Rate of the Two Groups

Mortality related to surgery and chemotherapy was higher in the LC group compared to the control group (19.2% vs 0%, P < 0.001). Among BC patients with LC, four (19.0%) developed recurrence and five (23.8%) had metastasis within 2 years. Of the four BC patients with LC who developed recurrence, three received anthracycline (doxorubicin) + taxane (docetaxel)- based therapy and one received other therapy (carboplatin + vinorelbine). Of the five BC patients with LC who had metastasis, four received anthracycline (doxorubicin) + taxane (docetaxel)- based therapy and one received other therapy (carboplatin + vinorelbine). No statistical difference was detected in the 2-year recurrence rate (P = 0.704) or 2-year metastasis rate (P = 0.797) among different chemotherapeutic regimens in BC patients with LC. All BC patients with LC who developed recurrence and/ or metastasis experienced disruption in chemotherapy. In the control group, five (3.8%) patients developed recurrence, and nine (6.9%) patients had metastasis within 2 years. Of the five BC patients without LC who developed recurrence, three received anthracycline (doxorubicin) + taxane (docetaxel)-based therapy, one received anthracycline (doxorubicin)-based therapy and one received other therapy (carboplatin + vinorelbine). Of the nine BC patients with LC who had metastasis, seven received anthracycline (doxorubicin) + taxane (docetaxel)-based therapy, one received anthracycline (doxorubicin)- based therapy and one received other therapy (carboplatin + vinorelbine). No statistical difference was detected in the 2-year recurrence rate (P = 0.095) or 2-year metastasis rate (P = 0.286) among different chemotherapeutic regimens in BC patients without LC. Four BC patients without LC developed recurrence underwent disruption in chemotherapy. Four BC patients without LC who developed metastasis experienced disruption in chemotherapy. The 2-year recurrence rate and 2-year metastasis rate were significantly higher in BC patients with LC compared to control patients (19.0% vs 3.8%, P = 0.022 and 23.8% vs 6.9%, P = 0.028). Three patients developed liver metastasis in BC patients with LC when three patients developed liver metastasis in the control group. BC patients with LC were vulnerable to developing liver metastasis than BC patients without LC (14.3% vs 2.3%, P = 0.036) (Table 4).

In univariate logistic regression analysis, the results showed that LC (the odds ratio [OR) = 6.833, 95% confidence interval [CI]: 1.28–36.482, P = 0.025), HER-2 positive (OR = 12.375, 95% CI: 1.401–109.277, P = 0.024) and disruptions in chemotherapy (OR =16.625, 95% CI: 2.883–95.876, P = 0.002) were significant risk factors for liver metastasis (Table 5). In subsequent multivariate analysis, which included other significant factors, LC (OR: 17.326, 95% CI: 2.164–138.707, P=0.007) and HER-2 positive (OR: 26.395, 95% CI: 2.237–311.466, P=0.009) remained significant risk factors for liver metastasis (Table 6).

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Table 4 Mortality Related to Surgery and Chemotherapy, Recurrent and Metastasis Rate of Breast Cancer Patients with and without Liver Cirrhosis

	Control Group	BC Patients with LC	P value
Mortality related to surgery and chemotherapy	0	5 (19.2%)	< 0.001
2-year recurrent rate	5 (3.8%)	4 (19.0%)	0.022
2-year metastasis rate	9 (6.9%)	5 (23.8%)	0.028
Liver metastasis	1	1	
Liver metastasis + Bone metastasis	1	0	
Liver metastasis + Pulmonary metastasis + Bone metastasis	1	2	
Pulmonary metastasis	1	0	
Pulmonary metastasis + Bone metastasis	1	0	
Bone metastasis	3	2	
Bone metastasis + Pancreatic metastasis	1	0	

Abbreviations: BC, breast cancer; LC, liver cirrhosis.

Table 5 Univariate Logistic Regression Analysis of the Significant Predictors for Liver Metastasis

Variables	B	SE	Wald	P value	OR	95% CI
Age	−0.100	0.060	2.737	0.098	0.905	0.804–1.019
Cirrhosis	1.922	0.855	5.057	0.025	6.833	1.28–36.482
ALT (U/L)	0.023	0.022	1.101	0.294	1.023	0.980–1.068
AST (U/L)	0.020	0.017	1.396	0.237	1.020	0.987–1.054
TBIL (μmol/L)	0.041	0.047	0.778	0.378	1.042	0.951–1.142
GGT (U/L)	0.010	0.006	3.092	0.079	1.010	0.999–1.021
ALP (U/L)	0.008	0.005	2.393	1.122	1.008	0.998–1.019
ALB (g/L)	−0.298	0.114	6.864	0.009	0.742	0.593–0.928
PT (s)	0.400	0.309	1.674	0.196	1.492	0.814–2.735
Cr (μmol/L)	−0.044	0.041	1.128	0.288	0.957	0.883–1.038
WBC ($\times 10^9$/L)	0.100	0.187	0.286	0.593	1.105	0.766–1.594
NEUT ($\times 10^9$/L)	0.010	0.244	0.002	0.966	1.011	0.627–1.630
LYM ($\times 10^9$/L)	0.459	0.638	0.472	1.582	1.582	0.453–5.520
Hb (g/L)	0.010	0.032	0.090	0.765	1.010	0.948–1.076
PLT ($\times 10^9$/L)	−0.011	0.006	2.999	0.083	0.989	0.978–1.001
Stage	0.934	0.630	2.199	0.138	2.546	0.740–8.753
ER positive	0.393	1.114	0.125	0.724	1.481	0.167–13.145
PR positive	−0.188	0.886	0.045	0.832	0.828	0.146–4.700
HER-2 positive	2.516	1.111	5.124	0.024	12.375	1.401–109.277
Disruption in chemotherapy	2.811	0.894	9.887	0.002	16.625	2.883–95.876

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; ALB, albumin; PT, prothrombin time; Cr, creatinine; WBC, white blood cell; NEUT, neutrophil; LYM, lymphocyte; Hb, hemoglobin; PLT, platelet; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2; OR, odds ratio; CI, confidence interval.

Table 6 Multivariable Logistic Regression Analysis of the Significant Predictors for Liver Metastasis

Variables	B	SE	Wald	P value	OR	95% CI
Cirrhosis	2.852	1.061	7.222	0.007	17.326	2.164–138.707
HER-2	3.273	1.259	6.756	0.009	26.395	2.237–311.466

Abbreviations: HER-2, human epidermal growth factor receptor-2; OR, odds ratio; CI, confidence interval.

Discussion

Randomized clinical trials often have strict enrollment criteria, and special populations, such as patients with severe underlying diseases (eg, cirrhosis, renal function failure) are frequently excluded. Therefore, the safety and efficacy of anticancer therapy in these special populations may differ from those determined in clinical trials. Clinical management recommendations for these patients are seldom evidence-based, sometimes inconsistent, and frequently lack clarity. Limited data are available regarding the safety and efficacy of surgery and chemotherapy in BC patients with LC. Despite the historically poor outcomes in LC patients, advances in the medical management of LC and improvements in life expectancy have increased the eligibility of these patients for multimodal therapy for BC. Surgery and chemotherapy constitute the cornerstone therapeutic regimen for BC patients.[15–18] However, due to the pathophysiological characteristics of LC, patients with LC are at a higher risk of developing AEs from surgery and chemotherapy.

It has been reported that the general postoperative morbidity in patients with cirrhosis is 30.1% after various surgeries, with a 30-day mortality rate of 11.6%.[19] The severity of LC and the type of operation can predict operative risk and patient outcomes.[8,9,19] However, previous studies did not include the common surgeries that BC patients undergo. In the present study, BC patients with LC primarily received modified radical mastectomy (88.5%). The postoperative morbidity in BC patients with LC was 26.9% (7/26), and the mortality rate was 3.8% (1/26). BC patients with LC, even those with compensated liver function (Child-Pugh A and B), may experience complications, even death, after operation (one patient died due to liver failure after surgery in the present study). Compared to the previously reported general postoperative morbidity and mortality rates in cirrhotic patients after various surgeries, the postoperative morbidity and mortality rates in BC patients with LC were lower in our study (26.9% vs 30.1% and 3.8% vs 11.6%, respectively).[19] Compared to BC patients without LC, the postoperative morbidity was higher in our study, and the mortality was not significantly different.

Chemotherapy regimens widely used in BC patients including cyclophosphamide, doxorubicin, bleomycin, and docetaxel, have been reported to have liver toxicity.[20–22] Patients with underlying liver diseases are at increased risk of severe treatment-related toxicity.[22,23] The liver is an important center of the absorption, distribution, active and inactive drug metabolites as well as elimination kinetics of most drugs.[23] The substantial decrease in the number of functioning hepatocytes or a decrease in enzyme activity because of alteration in the function of surviving cells and altered hepatic blood supply may impair drug metabolism in patients with LC.[24,25] Patients with LC may also be more sensitive to drug-related AEs. In the present study, our data indicated that the incidence of liver toxicity and other AEs precipitated by chemotherapy was significantly higher in BC patients with LC when compared to BC patients without any liver disease (73.1% vs 26.9%, $P < 0.001$, 15.4% vs 0%, $P = 0.001$, respectively). The incidence of severe AEs (grade 3 and grade 4) was also significantly higher in BC patients in terms of liver toxicity (50.1% vs 2.3%, $P < 0.001$) and other organ systems (7.7% vs 0%, $P = 0.027$). Therefore, even if they have normal liver function before chemotherapy, BC patients with LC may experience liver toxicity, including severe toxicity (grade 4), during chemotherapy. The incidence of myelosuppression was higher in BC patients with LC, although the difference was not statistically significant (84.6% vs 70.8%, $P = 0.225$). Most importantly, disruptions in chemotherapy attributable to AEs were more common in BC patients with LC than in those without any liver disease (46.2% vs 3.1%, $P < 0.001$). Moreover, this study detected that disruptions in chemotherapy were a risk factor for 2-year recurrence (OR = 16.634, 95% CI: 1.137–243.311, $P = 0.040$) and 2-year metastasis (OR = 15.119, 95% CI: 3.692–61.915, $P < 0.001$).

The present study suggests that the BC patients with LC carry a higher risk of recurrence and metastasis, particularly liver metastasis, compared toBC patients without liver disease. It was an interesting finding that BC patients with LC are particularly susceptible to liver metastasis. The present study revealed that cirrhosis is a significant risk factor for BC liver metastasis (OR: 17.326, 95% CI: 2.164–138.707, P=0.007). However, the mechanism remains unclear, and it is essential to closely monitor liver metastasis in BC patients with LC.

Disruptions in chemotherapy, including dose delays or dose reductions, may reduce the efficacy of chemotherapy or lead to treatment failure in BC patients.[26–29] In this study, all BC patients with LC who developed recurrence and/or metastasis experienced disruption in chemotherapy, with liver toxicity being the primary cause of chemotherapy-related mortality. AEs, particularly liver toxicity arising from BC treatment, can lead to the chemotherapy disruption, mainly therapy termination, which may contribute to the poor prognosis (cancer recurrence and/or metastasis) in BC patients with LC and even result in death. Determining the optimal therapy for BC patients with LC poses a significant challenge for clinicians. Safety and efficacy must be carefully taken into account, and clinicians should weigh the benefits and the risks when treating BC patients with LC. Although the prognosis of BC patients has improved with medical advances, the prognosis for special populations, especially those with underlying diseases such as cirrhosis, remains unsatisfactory. These special populations require additional attention and research, and strategies to improve their prognosis need to be determined.

Nonetheless, this study has certain limitations. As a small-scale retrospective study, it is insufficient to draw definitive conclusions. Large-scale prospective cohort studies are needed to further investigate these findings.

Conclusion

Taken together, the present findings indicate that BC patients with LC have compensated liver function (Child-Pugh class A and B) can undergo surgery for BC therapy with acceptable morbidity and mortality. Preoperative evaluation and perioperative care are essential components of therapy. BC patients with LC are more vulnerable to AEs, disruptions during chemotherapy, and a poor prognosis including death, recurrence and metastasis, especially liver metastasis.

Abbreviations

BC, breast cancer; LC, liver cirrhosis; NASH, non-alcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease (NAFLD); AEs, adverse events; WBC, white blood cell; NEUT, neutrophil; LMY, lymphocyte; PLT, platelet; Hb, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; ALB, albumin; PT, prothrombin time; Cr, creatinine; WBC, white blood cell; NEUT, neutrophil; LYM, lymphocyte; Hb, hemoglobin; PLT, platelet; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

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Disclosure

The authors report no conflicts of interest in this work.

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