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ORIGINAL ARTICLE

Conventional cytotoxic chemotherapy for gastrointestinal cancer in patients with cirrhosis: A multicentre case–control study

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Abstract

Background & Aims: Progresses in management make a higher proportion of cirrhotic patients with gastrointestinal (GI) cancer candidates to chemotherapy. Data are needed on the safety and liver-related events associated with the use of chemotherapy in these patients.

Methods: Forty-nine patients with cirrhosis receiving chemotherapy against GI cancer from 2013 to 2018 were identified in the French Health Insurance Database using ICD-10 codes K70-K74, and matched 1:2 to non-cirrhotic controls ($n = 98$) on age, tumour type and type of treatment. Adverse events (AE), dose tapering, discontinuation rate, liver-related events and survival rate were compared.

Results: Patients with cirrhosis (Child–Pugh A 91%) more often received lower doses (38.8% vs 7.1%, $p < .001$), without significant differences in terms of grade 3/4 AE or dose tapering rates (29.6% vs. 36.7%; 22.3% vs 24.4%, respectively). Treatment discontinuation rate was higher in patients with cirrhosis (23.3% vs. 11.3%, $p = .005$). Child–Pugh ($p = .007$) and MELD ($p = .025$) scores increased under chemotherapy. Five patients with cirrhosis (10.2%) had liver decompensation within 12 months, and 17.2% of deaths in the cirrhosis group were liver-related versus 0% in matched controls. WHO-PS stage > 1 (HR 3.74, CI95%: 2.13–6.57, $p < .001$), TNM-stage M1 (HR 3.61, CI 95%: 1.82–7.16, $p < .001$), non-colorectal cancer (HR 1.73, CI 95%: 1.05–2.86, $p = .032$) and bilirubin higher than 5 mg/dL (HR 2.26, CI 95%: 1.39–3.70, $p < .001$) were independent prognostic factors of 2-year mortality, whereas cirrhosis was not.

Conclusions: Chemotherapy should be proposed only in patients with compensated cirrhosis with close monitoring of liver function. Dose management remains challenging. Multidisciplinary management is warranted to improve these patients' outcomes.

KEYWORDS
chemotherapy, cirrhosis, gastrointestinal cancer, safety

1 | INTRODUCTION

Gastrointestinal (GI) cancers are frequent in patients with cirrhosis and represent a leading cause of mortality. Their occurrence is associated with several cancer risk factors such as obesity, as well as tobacco and alcohol consumption.[1,2] Liver fibrosis has been associated with an increased risk of GI cancers.[3,4]

As cirrhosis is related to a high risk of life-threatening events and impairment of drug metabolism, uncertainties exist regarding the therapeutic strategy in patients with cirrhosis and GI cancer. Progresses during the last decades in early screening of extensive fibrosis, prevention of liver events and improvement of liver function, make a higher proportion of patients with cirrhosis candidates to cytotoxic treatments and invasive procedures.

Despite therapeutic advances owing to the use of targeted therapies and immune checkpoint inhibitors, cytotoxic chemotherapy remains the backbone of treatment for GI cancers. Besides having hematologic and gastrointestinal side effects, several cytotoxic agents used in GI cancers may induce liver toxicity. Oxaliplatin has been associated with vascular liver diseases such as sinusoidal obstruction syndrome[5] and regenerative nodular hyperplasia.[6] Such lesions may lead to portal hypertension with increased postoperative morbidity and mortality after hepatectomy.[7,8] Irinotecan, 5-fluorouracil and cisplatin have been associated with the development of steatohepatitis and an increased risk of post-hepatectomy liver dysfunction.[9,10] Additional data are required to investigate the consequences of chemotherapy-induced liver injury in patients with underlying fibrosis or cirrhosis.

For oncologists, impaired hepatic function is usually characterized by the presence of jaundice.[11,12] While several studies have evaluated chemotherapy dose management in the context of biliary obstruction-induced jaundice, data are lacking in the more complex context of cirrhosis. Indeed, the accumulation of hepatocyte, biliary, vascular and architectural damage in chronic liver disease is a continuous process that results in progressive liver impairment and alteration of pharmacokinetics even before the appearance of jaundice.[13,14] Data on the safety profile of cytotoxic chemotherapy in patients with extensive fibrosis or compensated cirrhosis are currently lacking.

Considering the increasing need to treat patients with concurrent cirrhosis and GI cancer, the aims of this study were to analyse: a) the tolerance and management of cytotoxic chemotherapy, b) the occurrence of liver-related life-threatening events and c) causes of deaths and survival in patients with cirrhosis.

Key points

- Patients with cirrhosis are at competing risk of liver-related events and mortality, which may impact the oncological outcomes of GI cancers treated with cytotoxic chemotherapy.
- Careful multidisciplinary management is warranted when treating these patients.

2 | METHODS

2.1 | Study conduct

Collection and analysis of patients' data by the CHU of Lille was authorized under agreement no. 918110 of the French Data Protection Authority (*Commission Nationale de l'Informatique et des Libertés*) and exempt from IRB review according to French law due to the retrospective nature of the study (MR-004).

2.2 | Case–control study

All patients over 18 years old treated from January 1, 2013 to December 31, 2018 with cytotoxic chemotherapy for GI cancer (excluding hepatocellular carcinoma) in three hospital centres in Northern France were identified from the French Health Insurance Database (PMSI—Programme de Médicalisation des Systèmes d'Information).

Patients with cirrhosis were identified using ICD-10 codes K70 to K74 (listed in the Table S1). Individual medical records were then reviewed by two investigators (MB, MN), to confirm the diagnosis of cirrhosis based on available clinical, biological, morphological and/or histological data.

Two patients without cirrhosis were matched to each patient with cirrhosis using a two-step matching-selection process. First, we randomly sampled five control patients from the PMSI database. The random selection was performed with the following pre-established ranges or values: age of the cirrhotic patient ± 5 years; primary tumour site similar to that of the patient with cirrhosis; recruiting centre similar to that of the patient with cirrhosis. From these random-controlled matched patients, in a second step, we non-randomly selected two control patients who were the best fit for each patient with cirrhosis based on the type of therapy received (neo-adjuvant, adjuvant and palliative). Sex was not a matching criterion.

2.3 | Data collection and variables

The following variables were collected at the time of chemotherapy initiation: age, sex, patients' comorbidities, risk factors for chronic liver diseases (excessive alcohol consumption as defined by the World Health Organization [WHO], metabolic syndrome, chronic viral B or C hepatitis, auto-immune antibodies), WHO performance status, primary tumour site, metastatic sites, type of chemotherapy (neoadjuvant, adjuvant, palliative), date of chemotherapy initiation, type and dose of antineoplastics, laboratory values (haemoglobin, platelet count, leukocyte count, prothrombin time, international

normalized ratio [INR], albumin, aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT], bilirubin). For patients with cirrhosis, any previous episode of decompensation (ascites, jaundice, spontaneous bacterial peritonitis, variceal bleeding and hepatic encephalopathy) was recorded.

Within the first year, the following variables were collected at each quarterly evaluation by the patient's oncologist: date of evaluation, grade III/IV toxicities according to the U.S. National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, laboratory values (haemoglobin, platelet count, leukocyte count, prothrombin time, INR, albumin, AST, ALT, ALP, GGT, bilirubin), occurrence of tumour progression, liver-related events and death as well as causes of the latter.

2.4 | Endpoints

Safety was assessed based on adverse events (AE) leading to dose tapering or discontinuation of chemotherapy. Liver-related events were evaluated during the first 12 months after chemotherapy initiation and defined as the occurrence of ascites, jaundice, spontaneous bacterial peritonitis, variceal bleeding and hepatic encephalopathy. Underlying cirrhosis was considered the primary cause of liver-related events in the absence of significant liver tumour progression.

Overall survival (OS) was defined as the time from the date of chemotherapy initiation to the date of death from any cause or end of follow-up at 2 years. Recurrence-free survival (RFS) was defined in patients treated with neo-adjuvant or adjuvant chemotherapy, as the time from the date of surgery to the date of tumour recurrence, death from any cause or end of follow-up at 2 years. Progression-free survival (PFS) was defined in patients treated with palliative chemotherapy, as the time from the date of chemotherapy initiation to the date of tumour progression, death from any cause or end of follow-up at 2 years.

2.5 | Statistical analysis

Qualitative endpoints were described in terms of frequency and percentage. Quantitative parameters were described using the median and standard deviation. Normality of numerical parameters was checked graphically and tested using the Shapiro–Wilk test.

Safety was compared using mixed logistic models with a random effect to account for matching. Changes in biological parameters over time were compared between the two study groups using linear mixed models with time, group and a group/time interaction term as fixed effects and two random patient and block effects to account for correlation within each patient (repeated data) and matching blocks. Residuals were checked for normality to test the fit of the linear mixed models.

After matching, the survival curves represent the percentage of survival (overall and recurrence-free) in relation to the studied time point. The survival rate was determined using the Kaplan–Meier method. The impact of cirrhosis on overall and recurrence-free survival was analysed using a shared frailty model to account for matching block.

The significance level was set at 5%. We used SAS statistical software (version 9.4) to analyse the data (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Patient characteristics

Using the PMSI database, we identified 3854 patients treated with cytotoxic chemotherapy from January 2013 to December 2018, in the three participating centres. One hundred and twenty-four (3.2%) treated patients with the diagnosis codes K70–K74 were extracted. After reviewing the medical records, 75 patients were excluded for the following reasons: non-GI cancer ($n=32$), missing data in the medical record ($n=11$), loss of follow-up due to transfer to another clinic after the first administration of chemotherapy ($n=9$), recent history of another primary type of cancer ($n=9$), hepatocellular carcinoma ($n=8$), no cirrhosis ($n=2$) and miscellaneous reasons ($n=4$). Thus, 49 patients with cirrhosis were included. Using the above-mentioned algorithm, 245 matched-control patients were randomly selected, from whom, based on the indication (neoadjuvant, adjuvant or palliative), we non-randomly selected 98 patients without cirrhosis. The flow-chart diagram is available as Figure S1.

The characteristics of the 147 included patients are summarized in Table 1. As expected, age, primary tumour site and type of therapy indication were similar in the two groups. Colorectal cancer was the most frequent tumour type (40.8%), and chemotherapy was mostly palliative, for non-resectable locally advanced or metastatic disease (69.4%). Male sex was equally predominant in both groups (67%). General condition was well preserved (WHO-PS 0–1) in both groups (81.7 vs. 81.6%). In terms of metastatic sites, peritoneal metastases were more frequent in the control group (18.4% vs 6.1%, $p=.05$) than in the cirrhosis group, without significant differences for the other anatomical sites. Compared to patients without cirrhosis, patients with cirrhosis had lower platelet count ($p<.001$) and higher levels of serum bilirubin ($p=.001$) with median values remaining within normal ranges. In the control group, the probability of significant liver fibrosis was excluded: its median Fib-4 score was $1.5\pm.9$.

Cirrhosis was mainly related to excessive alcohol consumption in 38 patients (77.6%), among whom 37% still had ongoing excessive consumption. Child–Pugh (CP) and MELD scores were not available in 16 (32.7%) and 18 (36.7%) of the patients with cirrhosis, respectively; this happened in 17 patients because of missing data on coagulation tests. For patients with available scores, CP scores were A or B in 30 (90.9%) and 3 (9.1%) patients, respectively, and the median MELD was 8.2 (±1.8). Among patients with CP score A, two had a previous history of decompensation (one ascites and one variceal bleeding). None of the patients without available CP score (CP-NA) had previous or current episodes of clinical decompensation;

TABLE 1 Patient characteristics.

	Controls ($n=98$)	Cirrhosis ($n=49$)	p
Age	63.9 (8.2)	63.2 (8.8)	NA
Male sex	66 (67.3%)	33 (67.3%)	1
ECOG performance status			
0	28 (28.6%)	7 (14.3%)	.22
1	52 (53.1%)	33 (67.3%)	
2	14 (14.3%)	8 (16.3%)	
3	4 (4.1%)	1 (2%)	
Primary tumour site			
Colorectal	40 (40.8%)	20 (40.8%)	NA
Pancreas	14 (14.3%)	7 (14.3%)	
Oesophageal	13 (13.3%)	7 (14.3%)	
Gastric or gastroesophageal junction	13 (13.3%)	6 (12.2%)	
Small bowel	2 (2%)	1 (2%)	
Cholangiocarcinoma	16 (16.3%)	8 (16.3%)	
Metastatic site			
Liver	41 (41.8%)	24 (49%)	.49
Peritoneal	18 (18.4%)	3 (6.1%)	.049
Lung	18 (18.4%)	12 (24.5%)	.39
Lymph node	28 (28.6%)	11 (22.4%)	.55
Others	6 (6.1%)	2 (4.1%)	.72
Primary type of chemotherapy			
Neoadjuvant	14 (14.3%)	7 (14.3%)	NA
Adjuvant	16 (16.3%)	8 (16.3%)	
Palliative	68 (69.4%)	34 (69.4%)	
Risk factor for chronic liver disease			
Excessive alcohol consumption	13 (13.3%)	38 (77.6%)	<.001
Ongoing excessive consumption[a]		10 (37%)	
Metabolic Syndrome	24 (24.5%)	4 (8.2%)	
Others	0	5 (10.1%)	
Haemoglobin (g/dL)	12.2 (1.6)	12.6 (2)	.24
Platelet count ($\times 10^3/mm^3$)	288 (96)	227 (93)	<.001
Prothrombin time (%)	97 (9)	85 (12)	.07
Albumin (g/L)	40 (5)	38 (7)	.27
Bilirubin (mg/dL)	.46 (2.3)	.6 (.44)	.001
Child–Pugh score			
A5	–	21 (42.9%)	–
A6	–	9 (18.4%)	
Past decompensation (% in patients with CP-A)	–	2 (6.7%)	
B	–	3 (6.1%)	
Not available		16 (32.7%)	
MELD score	–	8.2 (1.8)	–
Receiving betablockers	–	16 (32.6%)	
Including propranolol		6 (12.2%)	

Note: Numerical variables are given as median (standard deviation).

Abbreviations: CPA, Child–Pugh A; NA, not applicable.

[a]Data available for 27 out of 38 patients with alcohol-related cirrhosis.

their median (±SD) values of albumin and bilirubin were 39 ± 8.6 g/L and .65 ± .4 mg/dL, respectively.

3.2 | Chemotherapy regimens

The most frequently used first-line chemotherapy regimens were: FOLFOX (5FU, leucovorin, oxaliplatin) in 60 patients (40.8%), GEMOX (gemcitabine, oxaliplatin) in 24 patients (16.3%), FOLFIRI (5FU, leucovorin, irinotecan) in 18 patients (12.2%) and FOLFIRINOX (5FU, leucovorin, irinotecan, oxaliplatin) in 15 patients (10.2%). Overall, platinum-based agents were used in 106 patients (72.1%) and irinotecan in 33 patients (22.4%). There was no significant difference between patients with cirrhosis and their matched controls in terms of first-line chemotherapeutic agents (Tables 2 and S2).

At the initiation of chemotherapy, patients with cirrhosis received more often a lower dose of chemotherapy than non-cirrhotic controls (38.8% vs 7.1%, respectively, $p<.001$), and a single-agent-based chemotherapy was more frequently used in the former than in the latter (22.4% vs. 10.2%, $p=.08$). Dose reductions were more frequent in patients with cirrhosis regardless of the number of chemotherapy agents (36% vs 0% when using a single-agent regimen, 41% vs 8% in a double-agent regimen, 33% vs 4% in a triple-agent regimen, Table S3). In cirrhotic and non-cirrhotic controls, dose-reductions were mostly applied on both agents in double agent regimens (8/12 and 4/5 in cirrhotic and non-cirrhotic patients with dose reduction, respectively) and on 2 drugs in triple-agent regimens (2/3 and 1/2 in cirrhotic and non-cirrhotic patients with dose reduction, respectively). Among 11 patients with cirrhosis treated with single-agent-based chemotherapy, 6 were treated with 5-FU or capecitabine for colorectal cancer; among them, only one patient could be escalated to FOLFIRI regimen after 3 months. The remaining 5 patients were treated with gemcitabine alone for metastatic pancreatic adenocarcinoma.

3.3 | Safety-related events

There was no significant difference in the frequency of grade 3 or 4 AE between patients with cirrhosis and their matched controls (total AE 36.7% vs. 29.6%, $p=.38$): hematologic AE (6.1% vs. 4.1%, $p=.58$), hepatic AE (6.1% vs. 11.2%, $p=.32$) and asthenia (16.3% vs. 15.3%, $p=.87$) (Table 3). When considering numerical biological variables, patients with cirrhosis displayed a higher decrease in haemoglobin values, with a difference becoming significant after 100 days of treatment ($p=.003$).

AE leading to dose tapering or discontinuation of chemotherapy in the two groups is given in Table 4. Follow-up time and number of evaluable patients at each time point were not different between the two groups. Dose tapering was not significantly different between the two groups (22.3% vs 24.4%, $p=.68$), even when only considering patients with full doses at initiation. Treatment discontinuation was more frequent in patients with cirrhosis than in their

TABLE 2 Initial chemotherapy regimen.

	Controls ($n=98$)	Cirrhosis ($n=49$)	p
Overall			
Single agent	10 (10.2%)	11 (22.4%)	.1
Double therapy	60 (61.2%)	29 (59.2%)	
Triple therapy	27 (27.6%)	9 (18.4%)	
Quadruple therapy	1 (1%)	0	
Full-dose regimen	91 (92.9%)	30 (61.2%)	<.001
Reduced dose regimen	7 (7.1%)	19 (38.8%)	
By primary tumour site			
Colorectal			.58
5-FU as single-agent	5 (13%)	6 (30%)	
FOLFOX	21 (52.5%)	10 (50%)	
FOLFIRI	9 (22.5%)	4 (20%)	
FOLFIRINOX	4 (10%)	0	
Targeted agents	11 (27.5%)	6 (30%)	
Pancreas			.12
FOLFIRINOX	8 (57.1%)	1 (14.3%)	
FOLFOX	0	1 (14.3%)	
Gemcitabine/ Nab-paclitaxel	1 (7.1%)	0	
Gemcitabine as single-agent	5 (35.7%)	5 (71.4%)	
Oesophageal			NA
FOLFOX	13 (100%)	7 (100%)	
Gastric or GEJ			.24
FLOT	5 (38.5%)	1 (16.7%)	
FOLFOX	5 (38.5%)	2 (33.3%)	
FOLFIRI	2 (15.4%)	1 (16.7%)	
FOLFIRINOX	0	2 (33.3%)	
5-FU/Cisplatin/ Trastuzumab	1 (7.7%)	0	
Small bowel			.08
FOLFOX	0	1 (100%)	
FOLFIRI	2 (100%)	0	
Cholangiocarcinoma			
Gemcitabine/ Oxaliplatin	16 (100%)	8 (100%)	NA

Abbreviations: FLOT, 5-FU, leucovorin, oxaliplatin, docetaxel; FOLFIRI, 5FU, leucovorin, irinotecan; FOLFIRINOX, 5FU, leucovorin, irinotecan, oxaliplatin; FOLFOX, 5FU, leucovorin, oxaliplatin; NA, not applicable.

matched controls (23.3% vs 11.3%, $p=.005$). Rates of administration of second-line chemotherapy did not differ (30.1% vs 38.8%, $p=.33$).

3.4 | Liver-related events and 2-year survival

Twelve months after chemotherapy initiation, 5 out of 49 patients with cirrhosis (10.2%) developed clinical liver decompensation versus 0 patients in the matched control group ($p=.003$). In patients for whom all items of CP score were available, liver decompensation occurred in 13.3% and 33.3% of patients with CP-A and CP-B, respectively. Chemotherapy was not resumed in patients after the development of liver decompensation. In patients with cirrhosis and repeated assessment of biological and clinical parameters ($n=22$ with at least two time points), CP ($p=.007$) and MELD ($p=.025$) scores increased under chemotherapy (Figure S2).

TABLE 3 Grade 3 or 4 adverse events.

Type	Controls ($n=98$)	Cirrhosis ($n=49$)	p
Total	29 (29.6%)	18 (36.7%)	.38
Hematologic (neutropenia, anaemia, thrombocytopenia)	4 (4.1%)	3 (6.1%)	.58
Liver enzyme elevation	11 (11.2%)	3 (6.1%)	.32
Digestive (nausea/vomiting, diarrhoea)	4 (4.1%)	5 (10.2%)	.14
Neurological (peripheral)	2 (2%)	0	.31
Fatigue	15 (15.3%)	8 (16.3%)	.87

Feasibility or outcome of surgery was not affected in 6 out of 7 cirrhotic patients treated with neoadjuvant chemotherapy, as they did not develop decompensation of cirrhosis. The remaining patient did not receive the preplanned surgery for oesophageal cancer due to the development of ascites and spontaneous bacterial peritonitis. Radiotherapy was performed after liver improvement in this latter case.

The 2-year OS, RFS and median PFS were similar in patients with cirrhosis and their matched controls (44.1 vs 44.2%, $p=.59$, Figure 1A; 64.3% vs 64.3%, $p=.95$, Figure 1B; 6.6 vs 5.9 months, $p=.33$, Figure 1C, respectively). After adjustment on WHO-PS, cirrhosis was still not associated with 2-year mortality. In patients with cirrhosis, death was attributed to liver-related events in 4 out of 23 deaths (17.4%). No death out of 51 occurred owing to liver-related events in the matched controls ($p=.008$). Liver-related deaths accounted for 23.1% (3/13) and 50% (1/2) of the deaths occurring in patients with CP-A and B scores at baseline, respectively.

In multivariate analysis, WHO-PS stage > 1 (hazard ratio [HR] 3.43, confidence interval [CI] 95%: 1.98–5.97, $p<.001$), TNM stage M1 (HR 3.61, CI 95%: 1.82–7.16, $p<.001$), non-colorectal cancer (HR 1.69, CI 95%: 1.02–2.79, $p=.04$) and bilirubin values higher than 5 mg/dL (HR 2.12, CI: 1.31–3.43, $p=.002$) were independently associated with 2-year mortality (Table S4).

4 | DISCUSSION

The present study shows that patients with cirrhosis may be treated for GI cancer with similar chemotherapy regimens as patients without cirrhosis; however, the dose should be reduced based on the choices of the physician. These tapered doses may explain, at least in part, the similar rates of grade 3 and 4 AE between groups, although treatment discontinuation was more frequent in patients

TABLE 4 Chemotherapy management during the first year.

	Time point 1		Time point 2		Time point 3		Time point 4		All time points combined		
	Controls	Cirrhosis	Controls	Cirrhosis	Controls	Cirrhosis	Controls	Cirrhosis	Controls	Cirrhosis	*p*
Follow-up (days, median ± SD)	64 ± 28	72 ± 24	146 ± 41	157 ± 35	218 ± 70	252 ± 48	292 ± 82	347 ± 81			
Number of patients time points assessed[a]	80 (81.6%)	45 (91.8%)	55 (56.1%)	28 (57.1%)	44 (44.9%)	18 (36.7%)	34 (34.7%)	12 (24.5%)	213	103	
No modification	26 (32.5%)	12 (26.7%)	19 (34.5%)	9 (32.1%)	19 (43.2%)	6 (33.3%)	19 (55.9%)	7 (58.3%)	83 (39%)	34 (33%)	.3
Dose increase or agent addition	1 (1.3%)	4 (8.9%)	1 (1.8%)	0	2 (4.5%)	0	0	0	4 (1.9%)	4 (3.9%)	.36
Dose tapering or agent withdrawal	27 (33.8%)	14 (31.1%)	20 (36.4%)	4 (14.3%)	2 (4.5%)	5 (27.8%)	3 (8.8%)	0	52 (24.4%)	23 (22.3%)	.68
Treatment interruption	15 (18.8%)	9 (20%)	9 (16.4%)	7 (25%)	5 (11.4%)	5 (27.8%)	5 (14.7%)	3 (25%)	24 (11.3%)	24 (23.3%)	.005
For toxicity	2 (2.5%)	2 (4.4%)	0	2 (7.1%)	0	1 (5.6%)	0	0	2 (.9%)	5 (4.9%)	.03
For physical deterioration	13 (16.3%)	7 (15.6%)	9 (16.4%	5 (17.9%)	5 (11.4%)	4 (22.2%)	5 (14.7%)	3 (25%)	22 (10.3%)	19 (18.4%)	.04

Abbreviations: NA, not applicable; SD, standard deviation.

[a]Patients were assessed only if treatment continuation was still indicated.

with cirrhosis. In a highly selected population, cirrhosis did not impact 2-year OS, RFS and PFS. However, liver-related events were more frequent in patients with cirrhosis than in those without, and liver-related mortality accounted for approximately 20% of deaths in the former. This study highlights the need for multidisciplinary collaboration between oncologists and hepatologists to increase access to and improve the management of chemotherapy in patients with GI cancer and cirrhosis.

Grade 3 and 4 AE, dose tapering and treatment discontinuation remained an important concern in patients with cirrhosis, despite initiating the chemotherapy with a lower dose, and a trend towards a higher use of single-agent-based chemotherapy in these patients compared to those without cirrhosis. These findings are consistent with those of studies evaluating the use of chemotherapy in patients with cirrhosis and advanced hepatocellular carcinoma.[15–17] The largest study including 204 patients indicated that the administration of the gemcitabine-oxaliplatin regimen led to a frequency of grade 3 and 4 AE of 44% and of discontinuation of 15.7%, rates close to those observed in the present study.[18] These safety-related events suggest an increased exposure to cytotoxic drugs in patients with cirrhosis, consistent with a modelling study that evaluated the pharmacokinetics of 133 drugs eliminated via the liver and revealed an approximately 2-fold increase in the area under the curve of drugs in CP-A patients.[19] Therefore, dose adjustments appear justified in patients with compensated cirrhosis,[20] which must be weighed against the risk of impaired efficacy in relation to dose reduction, as observed in patients with colorectal and pancreatic cancer.[21] As no recommendation from scientific societies is available for dose adjustments in cirrhotic patients, additional studies are warranted to optimize the dose, schedule and exposure to chemotherapy agents in cirrhotic patients.

The low prevalence (1.3%) of cirrhosis in the present cohort of approximately 4000 patients treated with chemotherapy raises the question of whether or not patients with cirrhosis have lower access to chemotherapy. Addressing this question needs to assess several factors. First, the prevalence of cirrhosis in the French general population is estimated between .3% and .7%.[22,23] Second, cirrhosis is expected to be more prevalent in patients with GI cancer, which have a higher exposure to metabolic syndrome and alcohol consumption than the general population, which is confirmed in the present study. The use of non-invasive tests for the diagnosis of advanced fibrosis would allow future studies to provide robust data on the prevalence of cirrhosis in patients with GI cancer.

The present study revealed a high proportion of liver-related life-threatening events associated with the worsening of biological liver parameters under chemotherapy. Approximately 10% of the patients with compensated cirrhosis developed liver decompensation 1 year following initiation of chemotherapy compared to 2%–3% of the patients with compensated cirrhosis not receiving such treatment. Considering this higher risk of liver decompensation, we do not support the use of chemotherapy in patients with CP-B. Although the sample size was limited and precludes

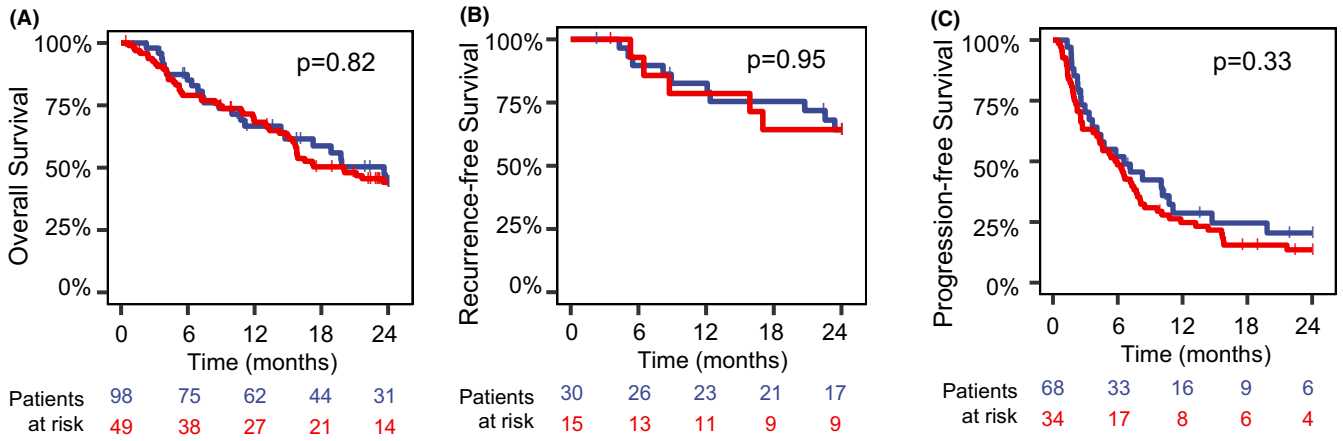

FIGURE 1 Comparative 2-year survival after chemotherapy initiation between patients with or without cirrhosis. Overall survival for the whole population (A), recurrence-free survival for patients with neoadjuvant or adjuvant chemotherapy (B) and progression-free survival (C) of patients with unresectable locally advanced or metastatic disease estimated with the Kaplan–Meier method. Patients without (blue line) or with (red line) cirrhosis were compared; the *p*-value was calculated using a shared frailty model to account for matching block.

reaching firm conclusions, our recommendation is in accordance with studies in patients with hepatocellular carcinoma and treated with tyrosine kinase inhibitors. These studies indicated an impaired survival in patients with CP-B compared to those with CP-A.[24] In this context and as observed in the present study, the main contributor to increased mortality in patients with cirrhosis is the increased risk of liver-related death. The implementation of measures to prevent the exacerbation of liver injury is needed. These may include management of alcohol use disorder in patients with alcohol-related cirrhosis, antiviral therapy in patients with viral hepatitis, prophylactic use of beta-blockers in case of portal hypertension and early therapeutic intervention when liver-related events occur. Assessing the cause of decompensation is a complex issue in these patients, with the interaction between established factors of liver decompensation, tumour characteristics and chemotherapy effects. It is interesting to note that only bilirubin was associated with mortality, and not albumin or prothrombin time, parameters of liver function that are not affected by biliary tract injury. Thus, we are not able to propose a driving mechanism for decompensation in such patients, as several contributing factors may be intricated. Additional studies are now needed to identify early markers to predict liver decompensation under chemotherapy.

This study reports the risk of liver decompensation using cytotoxic chemotherapy for non-HCC cancers. Whether this risk would be similar using targeted therapies or immunotherapies is currently unknown. Data in cirrhotic patients with HCC are conflicting. In post-hoc analyses of the SHARP trial, hepatic function remained stable over the course of sorafenib therapy, without significant difference in median bilirubin changes compared to patients in the placebo group.[25] Conversely, in a retrospective real-life study, the worsening of liver function using atezolizumab-bevacizumab was reported in 10.8% of patients with adequate baseline liver function as per the pivotal study's criteria, with rates of new onset/aggravation of ascites or hepatic encephalopathy in 9.5% and 1.4% of patients, respectively.[26] While this may appear similar to the 10% rate in our study, caution is warranted as intra-hepatic and vascular tumour burden and progression may be additional factors contributing to the occurrence of liver decompensation in patients with HCC. In the context of increasing use of targeted therapies and immunotherapy in non-HCC GI cancers, additional studies are needed to assess the risk of decompensation in cirrhotic patients in this context.

The present study had several limitations: the sample size, as well as the lack of data on on-treatment alcohol consumption, preplanned monitoring of biological and clinical liver parameters, a standardized action plan in case of liver-related events and insufficient power to identify factors associated with post-chemotherapy decompensation. We did not use the therapeutic regimen as a matching criterion. Such approach allowed us to determine that the presence of cirrhosis did not affect the choice of the therapeutic regimen. We acknowledge this may have introduced a risk of bias in the analysis. However, the lack of differences in therapeutic regimens does not support such bias. Oncological outcomes were not significantly different between patients with cirrhosis and those without cirrhosis. This should be considered as a preliminary result, as we acknowledge the potential biases resulting from merging patients with different cancer locations and tumour stages. Larger studies are now needed to confirm these results according to primary tumour type and chemotherapy indication. Finally, nutritional status, sarcopenia and frailty are crucial prognostic determinants in decompensated cirrhosis.[27] Data are less clear in compensated cirrhosis in whom prevalence is lower. As retrospective evaluation could be a source of biased conclusions, future studies with adequate sample size and matched controls should include prospective and standardized assessment of these parameters. These limitations highlight the urgent need for a multidisciplinary approach to optimize the therapeutic management of these complex patients who are at risk of dying from multiple competing mechanisms.

In conclusion, chemotherapy should be proposed only in patients with compensated cirrhosis while the close monitoring of liver function is ensured. The reduction of the dosage seems to be necessary in patients with cirrhosis and GI cancer. Despite this, dose tapering and treatment discontinuation remain challenging. Multidisciplinary management is needed when treating a patient with cirrhosis with chemotherapy for GI cancer.

AUTHOR CONTRIBUTIONS

Massih Ningarhari and Anthony Turpin conceived and designed the study. Massih Ningarhari and Marlène Bertez collected the data and performed the analysis. Anne Ploquin, Nicolas Bertrand, Christophe Desauw, Stéphane Cattan, Pascale Catala, Hélène Vandamme and Claire Cheymol provided the data. All authors contributed to the interpretation. Massih Ningarhari, Marlène Bertez and Anthony Turpin drafted the work. All authors critically revised the study for intellectual content and approved the final version for publication. All authors agree to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of this study are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or non-financial interests to disclose. The authors have no competing interests to declare that are relevant to the content of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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