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Retrospective Study

Retrospective analysis of irinotecan-based *vs* oxaliplatin-based regimens for neoadjuvant chemotherapy in patients with resectable colorectal liver metastasis in China

Liu W *et al*. Neoadjuvant irinotecan in resectable CRLM

Abstract

BACKGROUND

Neoadjuvant chemotherapy (NC) improves the survival outcomes for selected patients with colorectal liver metastasis (CRLM). The benefits of irinotecan-based regimens are still under debate.

AIM

To compare the benefits of irinotecan- and oxaliplatin-based regimens in patients with resectable CRLM.

METHODS

From September 2003 to August 2020, 554 patients received NC and underwent hepatectomy for CRLM. Based on a 1:1 propensity score matching (PSM) model, 175 patients who received irinotecan were matched to 175 patients who received oxaliplatin to obtain two balanced groups regarding demographic, therapeutic and prognostic characteristics.

RESULTS

Chemotherapy was based on oxaliplatin in 353 (63.7%) patients and irinotecan in 201 (36.3%). After PSM, the 5-year progression-free survival (PFS) and overall survival (OS) rates with irinotecan were 18.0% and 49.7%, respectively, while the 5-year PFS and OS rates with oxaliplatin were 26.0% and 46.8%, respectively. Intraoperative blood loss, operating time, and postoperative complications differed significantly between the two groups. In the multivariable analysis, carbohydrate antigen 19-9, RAS mutation, response to NC, tumor size > 5 cm, and tumor number > 1 were independently associated with PFS.

CONCLUSION

In NC in patients with CRLM, irinotecan was similar to oxaliplatin in survival outcomes, but irinotecan was superior regarding operating time, intraoperative blood loss, and postoperative complications.

Key Words: Colorectal cancer; Liver metastasis; Liver resection; Neoadjuvant chemotherapy

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Core Tip: This was the first retrospective cohort study to investigate irinotecan-based regimens for neoadjuvant chemotherapy in patients with colorectal liver metastasis (CRLM) in China. It highlighted the benefits of irinotecan and might contribute to modifying the treatment guidelines for CRLM. Chemotherapy was based on oxaliplatin in 353 (63.7%) patients and irinotecan in 201 (36.3%). After propensity score matching, the 5-year progression-free survival (PFS) and overall survival (OS) rates with irinotecan were 18.0% and 49.7%, respectively, while the 5-year PFS and OS rates with oxaliplatin were 26.0% and 46.8% respectively.

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy and is the second leading cause of cancer-related mortality[1]. Liver is the most common site of metastatic involvement, and 25%-30% of CRC patients present with metastatic diseases initially. The long-term survival outcome has been significantly improved by radical resection of primary and metastases tumor. The overall survival (OS) increased from 36% to 58% at 5-year and 23% to 36% at 10-year, respectively[2,3]. Advances in surgical techniques have improved safety dramatically, resulting in perioperative mortality rates < 5%[4].

Currently, the administration of neoadjuvant chemotherapy (NC) in resectable colorectal liver metastasis (CRLM) patients is increasing as it can increase the radical resection rate and treat occult metastases[5]. 5-Fluorouracil (5-Fu) was previously one of the most common anticancer drugs for CRLM. FOLFIRI (irinotecan, 5-Fu and leucovorin) or FOLFOX (oxaliplatin, 5-Fu and leucovorin) have been proven more effective. By combined to antibodies targeting epidermal growth factor receptor and vascular endothelial growth factor, response rate of about 20% observed in the new era of modern chemotherapy have been greatly increased. Nevertheless, it has been shown that systemic chemotherapy for CRLM might cause injury to the nontumoral liver parenchyma. Sinusoidal obstruction syndrome (SOS) has been identified as being a complication to oxaliplatin-based chemotherapy[6]. Steatohepatitis was considered to be associated with irinotecan-based chemotherapy, especially in obese patients[7]. Because of impaired remnant liver function, chemotherapy-induced liver injury is a major cause of morbidity and mortality after hepatic resection.

For resectable CRLM, oxaliplatin-based regimens have been preferred to irinotecan-based regimens as the first-line treatment because of less alopecia and gastrointestinal toxicity[8]. Irinotecan has been administered to patients with resectable CRLM was absent for supporting evidence, and survival outcomes whether were improved remains under debated. The present study investigated whether irinotecan might improve progression-free survival (PFS) or OS in patients with resectable CRLM.

MATERIALS AND METHODS

Patient eligibility

This study collected the data from CRLM patients who received NC and underwent hepatic resection between September 2003 and August 2020 at the Hepatopancreatobiliary Surgery Department of Peking University Cancer Hospital. The demographic and clinical data were retrospectively obtained from a prospective patient database. The inclusion criteria were: (1) Evaluated to be resectable by a multidisciplinary team (MDT) that consisted of surgical oncologists, radiologists and

medical oncologists; (2) Received NC and underwent hepatic resection; (3) No other simultaneous malignancies; (4) 19-80 years of age; and (5) Eastern Cooperative Oncology Group performance status < 2. Patients who underwent only ablation or palliative hepatic resection (R2) were excluded. This study was approved by the Ethics Committee of Beijing Cancer Hospital (No. 2021YJZ06-GZ01), and the requirement for informed consent was waived.

Pretreatment evaluation

All patients were evaluated by physical examination, routine hematology, biochemistry analyses and tumor marker including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (Ca19-9) levels before treatment. According to standard clinical protocols, computed tomography or magnetic resonance imaging of the abdomen and chest was performed for preoperative staging and evaluation of liver metastasis. In addition, positron emission tomography was performed to rule out any extrahepatic metastasis.

Treatment

The NC regimens consisted mainly of 5-Fu, leucovorin and oxaliplatin, or 5-Fu, leucovorin and irinotecan, with or without bevacizumab or cetuximab. There were 353 patients who received a regimen based on oxaliplatin and 201 patients who were treated with a regimen based on irinotecan. Based on World Health Organization criteria, the response to NC was classified and agreed to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). MDT discussion assess the treatment response and the possibility of surgery. If the patient presented with disease progression, a new second-line chemotherapy regimen was recommended.

In surgical treatment, the technical criteria for resectability related to the liver remnant after resection were: (1) Preserving two contiguous segments; (2) Preserving adequate vascular inflow, outflow, and biliary drainage; and (3) Preserving adequate future liver remnant volume (30% in normal liver and 40% in patients with

preoperative chemotherapy)[9]. Major hepatic resection was defined to be any resection of three or more segments. All the patients underwent hepatic resection and primary tumor resection. All the specimens were examined for pathological diagnosis after surgery.

Statistical analysis

The continuous variables were expressed using median and range, and the categorical variables were expressed as number (*n*) and frequency (%). The c^2 or Fisher's exact test were used to compare categorial variables between groups. While the Mann-Whitney *U* test was afford to compare the continuous variables between groups. Propensity score matching (PSM) was applied to compensate for the biases between the irinotecan and the oxaliplatin groups in the unmatched cohort with a matching ratio of 1:1 by the nearest neighbor method. The 0.05 was set to be caliper value. The imbalance before and after PSM was assessed by the standardized mean difference. The following variables were included in the PSM model: Age, sex, primary N stage, number of liver metastases, preoperative CEA/Ca19-9, preoperative clinical risk score (CRS) of Fong[10], RAS mutation status, cycles of NC, major hepatic resection, intraoperative radiofrequency ablation combined with hepatic resection, adjuvant chemotherapy, and response to NC. Short-term results were compared between the irinotecan and oxaliplatin groups before and after PSM, such as loss of intraoperative blood, red blood cell (RBC) transfusion during intraoperative, operating time and Clavien-Dindo grade of general or surgical complications. PFS was defined as the time from treatment to recurrence, disease progression, or death, whichever occurred first[11]. OS was defined as the interval between hepatic resection and the date of death or last follow-up. Kaplan-Meier survival analysis compared the PFS and OS before and after PSM using the log-rank test. Uni- and multivariable analyses were conducted by Cox proportional hazards model and identified the independent prognostic factors of PFS after PSM. Significance level was 0.05, SPSS version 23 was used for statistical analysis (IBM, Armonk, NY, United States).

RESULTS

Comparison of irinotecan- and oxaliplatin-treated patients before PSM

We enrolled a total of 554 CRLM patients, with 201 in the irinotecan group and 353 in the oxaliplatin group. Primary N stage, timing of liver metastases, biological agent, staged resection, and operating time were significantly different between the two groups (all $P < 0.005$) (Table 1).

Long-term outcomes before PSM

The median follow-up was 41 mo. The intrahepatic and extrahepatic recurrence rates were not significantly different between the irinotecan and oxaliplatin groups. There were no significant differences in 1-, 3- or 5-year PFS and OS rates (all $P > 0.05$; Figures 1A and 1B). In the irinotecan group, the median PFS was 14.0 mo and the 5-year PFS was 25.2%, respectively. The median OS was 65 mo and 5-year OS rates was 54.0%, respectively. In the oxaliplatin group, the median PFS was 12.5 mo and 5-year PFS was 22.0%, respectively. The median OS was 46 mo and 5-year OS was 39.8%, respectively.

Comparison of irinotecan- and oxaliplatin-treated patients after PSM

After PSM for the significantly different preoperative and prognostic factors between the two groups, 175 patients from the irinotecan group and 175 from the oxaliplatin group were considered for the matched analyses. When the biases associated with the differences in primary N stage, timing of liver metastases, biological agent, staged resection, intraoperative RBC transfusion, and operating time were removed by PSM, differences in intraoperative blood loss, operating time and postoperative complications were observed (Table 2).

Long-term outcomes after PSM

The median follow-up was 42 mo. The 1-, 3- and 5-year OS rates were higher in the irinotecan group than in the oxaliplatin group, while the reverse trend was observed for

PFS, but the differences were not significant (P > 0.05; Figures 2A and 2B). In the irinotecan group, the 5-year PFS and OS rates were 18.0% and 49.7%, respectively, and the median PFS and OS were 13.5 and 49 mo, respectively. In the oxaliplatin group, the 5-year PFS and OS rates were 26.0% and 46.8%, respectively, and the median PFS and OS were 12.0 and 57 mo, respectively.

Building Cox proportional hazards model

Multivariable Cox regression analysis was performed for the PSM cohort. In the univariate analysis, primary tumor location, synchronous liver metastases, tumor size > 5 cm, tumor number > 1, CRS 3-5, concomitant ablation, bilobar distribution, Ca 19-9 > 100 U/mL, RAS mutation, and response rate were associated with PFS (P < 0.05) (Table 3). In the multivariate analysis, tumor size > 5 cm, tumor number > 1, RAS mutation, Ca 19-9 > 100 U/mL, and response rate to NC were independently associated with PFS (all P < 0.05).

DISCUSSION

Compared with 5-Fu alone, irinotecan-based preoperative chemotherapy increased the response rates up to 39%[12], and oxaliplatin improved the response rate from 22% to 51%[13]. With newly developed biological agents, further significant benefits were achieved. Almost 60% of populations were evaluated to be tumor response by combining oxaliplatin-based or irinotecan-based chemotherapy with such targeted agents[14]. In the present study, the 5-year PFS and OS rates were 25.2% and 54.0% for the irinotecan group, respectively. In the oxaliplatin group, the 5-year PFS and OS rates were 22.0% and 39.8%, respectively. Our study was the first retrospective cohort analysis to compare the survival outcomes of irinotecan and oxaliplatin in patients with CRLM.

During the past few years, perioperative chemotherapy for CRLM has been developed remarkably. NC is recommended for resectable CRLM patients to increase the possibility of radical resections. It also might crush the occult metastasis in the liver

remnant. Moreover, NC could test whether cancer cells are chemosensitive *in situ*. According to the responses mentioned above, physicians might determine the individualized adjuvant chemotherapy regimen and identify patients who would not benefit from immediate hepatic resection because of tumor progression. Nevertheless, it is still controversial whether NC should be applied for all patients with resectable CRLM. It was reported that a significant improvement in PFS was observed for resectable CRLM patients after NC with FOLFOX4 by the EORTC Intergroup Trial 40983. In contrast, 64% of CRLM patients achieved an objective radiological response after NC, and disease-free survival also improved significantly according to a systematic review of 23 studies comprising 3278 patients. In the present study, tumor size > 5 cm, tumor number > 1, RAS mutation, Ca 19-9 > 100 U/mL, and response to NC were independent factors for PFS. This was consistent with previous studies. Hepatic resection is considered a standard treatment for CRLM patients, including special populations, such as those treated with hyperthermic intraperitoneal chemotherapy (HIPEC) and pregnant women[15,16]. HIPEC can be administered before or after surgery, and future studies should examine which HIPEC strategy, and combined with which chemotherapy regimen, would achieve better outcomes.

Oxaliplatin- and/or irinotecan-based NC might cause histological damage, vascular lesions, or steatohepatitis although there are conflicting results in the literature[6,7]. Chemotherapy-induced liver injury could reduce the function of the future remnant liver with an increase in postoperative complications[17]. Non-parenchymal-sparing strategies have been advocated for radical resection of CRLM and the outcomes associated with these strategies have been reported. Nakano *et al*[17] have reported that major hepatic resection for patients with CRLM with SOS might increase the risk of postoperative complications. Sinusoidal lesions have been associated with an increased blood requirement and higher postoperative liver failure[18,19].

Many studies have attempted to identify predictive factors for chemotherapy-induced liver damage[20]. It is reported that the following could induce SOS: High γ-glutaryl transferase levels, low platelet counts, high aspartate aminotransferase to

platelet ratios, and enlarged spleen[21,22]. However, prospective studies are required to confirm the relevance of these factors, and a combination of parameters may provide evidence to establish a diagnosis of SOS preoperatively. Bevacizumab offers an opportunity to prevent SOS and reduces the incidence from 46% to 5% when added to preoperative chemotherapy[23]. It was hypothesized that endothelial cells might secret matrix metalloprotease-9 (MMP-9) induce SOS from in murine model. Bevacizumab might improve SOS by inhibiting vascular-endothelial-growth-factor-dependent induction of MMP-9 and subsequent matrix degradation[24]. The present study had some limitations. Firstly, it was an retrospective cohort study without randomizing for enrolled patients. Secondly, the included patients were limited after PSM. The sample size should be enlarged in a randomized controlled trial. Thirdly, a validation group would strengthen the present conclusions.

CONCLUSION

In NC for CRLM, irinotecan was similar to oxaliplatin in improving the survival outcomes, but irinotecan was superior in reducing operating time, intraoperative blood loss, and postoperative complications.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) represents an important disease burden worldwide, being the third most common malignancy and the second leading cause of cancer mortality. Many patients are *de novo* metastatic at presentation, and liver metastasis is common in CRC. In selected patients with colorectal liver metastases (CRLM) (*i.e.,* liver as the only metastatic site), surgery can be performed directly, but some patients with resectable CRLM will require neoadjuvant chemotherapy (NC) to increase the radical resection rate and treat occult metastases. On the other hand, chemotherapy can cause liver injury that will lead to impaired remnant liver function.

Research motivation

For resectable CRLM, oxaliplatin-based regimens have been preferred to irinotecan-based regimens as the first-line treatment because of lower occurrences of alopecia and gastrointestinal toxicity. Irinotecan has been suggested for patients with resectable CRLM, but data for such patients are limited and whether outcomes are improved remains debatable. Therefore, even though NC improves the survival outcomes for selected patients with CRLM, the benefits of irinotecan-based regimens are still under debate.

Research objectives

This study investigated the benefits of irinotecan- *vs* oxaliplatin-based NC regimens in patients with resectable CRLM.

Research methods

At a single hospital in China, 554 patients received NC and underwent hepatectomy for CRLM from September 2003 to August 2020. In order to manage confounding factors, a 1:1 propensity score matching (PSM) was performed. Overall survival (OS), progression-free survival (PFS), intraoperative blood loss, operation time, and postoperative complications were compared between the two groups.

Research results

In the present study, NC regimens were based on oxaliplatin in 353 (63.7%) patients and on irinotecan in 201 (36.3%). Finally, 175 patients who received irinotecan-based NC were matched to 175 patients who received oxaliplatin-based NC. Hence, the two groups were balanced regarding demographic, therapeutic, and prognostic characteristics. After PSM, the 5-year PFS rates were 18.0% for irinotecan-based NC and 26.0% for oxaliplatin-based NC, while the 5-year OS rates were 49.7% for irinotecan-based NC and 46.8% for oxaliplatin-based NC. Intraoperative blood loss (201 *vs* 264 mL, $P = 0.024$), operation time (188 *vs* 208 min, $P = 0.012$), and postoperative complications

(28.6% *vs* 42.3%, *P* = 0.019) all favored the irinotecan-based NC group. In the multivariable analysis, carbohydrate antigen 19-9 [hazard ratio (HR) = 1.52, 95% confidence interval (CI): 1.03-2.24], RAS mutation (HR = 1.47, 95%CI: 1.13-1.91), response to NC (HR = 1.83, 95%CI: 1.21-2.76), tumor size > 5 cm (HR = 1.48, 95%CI: 1.06-2.06), and tumor number > 1 (HR = 1.45, 95%CI: 1.08-2.15) were independently associated with the PFS.

Research conclusions

In patients with CRLM, the PFS and OS are similar between irinotecan- and oxaliplatin-based NC. On the other hand, irinotecan-based NC was superior to oxaliplatin-based NC in terms of shorter operation time, smaller intraoperative blood loss, and fewer postoperative complications.

Research perspectives

This retrospective cohort analysis was the first to compare the OS and PFS of irinotecan-based NC *vs* oxaliplatin-based NC in patients with CRLM. Even though these results can help determine the best options for patients with CRLM, multicenter randomized controlled trials would be required for confirmation. In addition, future studies could examine different dosing strategies in patients with CRLM.

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