Oncological Outcomes of Patients with Peritoneal Metastasis–only Colorectal Cancer Treated with First-line Bevacizumab and FOLFIRI through Irinotecan Dose Escalation According to *UGT1A1* Polymorphism: Compared to Liver Metastasis–only, and Lung Metastasis–only

Ching-Chun Li

Kaohsiung Medical University <https://orcid.org/0000-0001-8459-2426>

Tsung-Kun Chang

Kaohsiung Medical University Hospital: Kaohsiung Medical University Chung Ho Memorial Hospital

Yen-Cheng Chen

Kaohsiung Medical University Hospital: Kaohsiung Medical University Chung Ho Memorial Hospital

Hsiang-Lin Tsai

Kaohsiung Medical University Hospital: Kaohsiung Medical University Chung Ho Memorial Hospital

Ching-Wen Huang

Kaohsiung Medical University Hospital: Kaohsiung Medical University Chung Ho Memorial Hospital

Wei-Chih Su

Kaohsiung Medical University Hospital: Kaohsiung Medical University Chung Ho Memorial Hospital

Cheng-Jen Ma

Kaohsiung Medical University Hospital: Kaohsiung Medical University Chung Ho Memorial Hospital

Tzu-Chieh Yin

Kaohsiung Municipal Ta-Tung Hospital: Kaohsiung Municipal United Hospital

Po-Jung Chen

Kaohsiung Municipal Hsiao-kang Hospital: Kaohsiung Municipal Siaogang Hospital

Jaw-Yuan Wang (✉ cy614112@ms14.hinet.net)

Kaohsiung Medical University Hospital <https://orcid.org/0000-0002-7705-2621>

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Abstract

Background:

The prognosis of metastatic colorectal cancer (mCRC) depends on the metastatic site and systemic therapy regimen. Peritoneal metastases are associated with a relatively unfavorable prognosis among patients with mCRC. In this article, we present the treatment outcomes of patients with peritoneal carcinomatosis (PC)–only, liver metastasis (LiM)–only, and lung metastasis (LuM)–only CRC.

Methods:

Overall, 206 mCRC patients with single-site metastasis and who had received treatment from January 2014 to December 2018 were recruited. Among 206 patients with mCRC, 15 had PC-only mCRC, 145 had LiM-only mCRC, and 46 had LuM-only mCRC. They attended regular follow-ups until November 2020, and the median follow-up period was 24.7 months (5.1–41.3 months). Patients' characteristics, including clinical data, gene mutation profiles, and clinical outcomes, were evaluated. All patients with PC-only CRC were treated with first-line bevacizumab and FOLFIRI, and the irinotecan dose escalation depended on *UGT1A1* polymorphism.

Results:

Of the 206 patients, no statistical difference was observed between the PC-only, LiM-only, and LuM-only groups in terms of age, primary tumor location, *RAS* mutation status, *BRAF* mutation status, and epidermal growth factor receptor overexpression (all $P > 0.05$). *KRAS* mutations were detected in two (16.7%) patients with PC-only CRC, 39 (36.4%) patients with LiM-only CRC, and 12 (36.4%) patients with LuM-only CRC. *NRAS* mutations were detected in one (8.3%) patient with PC-only CRC, six (7.3%) patients with LiM-only CRC, and two (7.1%) patients with LuM-only CRC. *BRAF* mutations were detected in two (15.4%) patients with PC-only CRC, seven (6.9%) patients with LiM-only CRC, and one (2.9%) patient with LuM-only CRC. Patients with PC-only CRC had a median progression-free survival (mPFS) of 18.0 months and a median overall survival (mOS) of 24.6 months. Patients with LiM-only or LuM-only CRC had mPFS of 18.2 and 26.6 months and mOS of 25.0 and 44.5 months, respectively. No significant differences regarding PFS and OS (both $P > 0.05$) between the three groups of patients with mCRC were observed.

Conclusions:

A PC-only status is considered to be a challenge in the treatment of patients with mCRC. Our study revealed that in patients with PC-only mCRC had a higher incidence of *BRAF* mutations, and treatment of first-line bevacizumab and FOLFIRI through irinotecan dose escalation according to *UGT1A1* polymorphism could confer such patients with comparable outcomes to that of patients with LiM-only and LuM-only mCRC. However, further prospective randomized trials on patients with peritoneal metastatic mCRC should be conducted to verify the findings of this retrospective study.

Introduction

Colorectal cancer (CRC) is a major cause of cancer-related deaths worldwide; over 1 million new cases are diagnosed annually [1–2]. Approximately 20%–25% of patients with CRC present with metastases at their initial diagnosis, and the most common sites of metastases from CRC are the liver, lung, and peritoneum [3]. The prognosis of metastatic colorectal cancer (mCRC) depends on the specific metastatic sites involved; a combination of systemic therapy and metastasectomy could provide the best survival rate [4, 5]. Peritoneal carcinomatosis (PC)–only CRC has a poor prognosis and is often considered to be a terminal condition. A comparison between isolated site metastasis between peritoneum, liver, and lung metastases reported median overall survival (OS) periods of 16.3 months in PC-only CRC, 19.1 months in liver metastasis CRC, and 24.6 months in lung metastasis CRC [6].

Treatment of mCRC has significantly improved in terms of progression-free survival (PFS) and OS due to the use of new chemotherapeutic and molecular target agents. The association between clinical outcomes and the gene mutations of the *Kras*, *NRAS*, and *BRAF* genes has become more clearly understood. *RAS* mutation status has been reported to exhibit a significant association with the survival outcomes of patients with liver metastasis (LiM)-only mCRC [7].

The current standard first-line chemotherapy for patients with mCRC includes fluoropyrimidine-based doublet chemotherapy—FOLFOX or FOLFIRI—plus bevacizumab [3]. A retrospective study revealed that patients with mCRC who received escalated doses of irinotecan according to uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) genotyping exhibited favorable clinical responses and outcomes [8]. Recently, our prospective, randomized study also suggested that if patients with mCRC, regardless of their *KRAS* gene status, receive *UGT1A1* genotyping, they can tolerate escalated doses of irinotecan and potentially achieve a more favorable clinical outcome without significantly increased toxicity [9, 12]. Furthermore, the oncological outcomes of patients with *BRAF*-mutated mCRC treated using FOLFIRI plus bevacizumab with irinotecan dose escalation as a first-line therapy are acceptable with tolerable adverse events; this approach may be a feasible treatment option for such patients [10]. In the current retrospective study, we investigated the clinical outcomes of patients with PC-only mCRC who received first-line bevacizumab and FOLFIRI with irinotecan dose escalation according to *UGT1A1* polymorphism.

Methods

Patients' characteristics

From a single institution, 398 patients with stage IV CRC who had received treatment between January 2014 and December 2018 were selected. Patients with record duplications ($n = 5$) or neuroendocrine tumors ($n = 1$) were excluded, and those with two metastatic sites ($n = 159$) or other metastatic sites ($n = 16$) were also excluded. For the study, 15 (15/398, 3.8%) patients consecutively diagnosed as having PC-only CRC, 145 (145/398, 36.4%) patients diagnosed as having LiM-only CRC, and 46 (46/398, 11.6%) patients diagnosed were as having lung metastasis (LuM)–only CRC were recruited; the flow diagram of

patient selection is presented in Figure 1. A case series analysis was performed using a routinely updated and maintained electronic medical record database. Demographic data included age at diagnosis, sex, primary tumor location, and gene mutation. All aspects of this study were approved by the institutional review board of Kaohsiung Medical University Hospital. Finally, this study was a retrospective review of 206 patients with mCRC, and written informed consent was obtained from all patients (KMUHIRB-E(I)-20200036). The responses were classified by a radiologist according to RECIST Version 1.1 [10]. DNA extraction for direct sequencing of *KRAS/NRAS* and immunohistochemical (IHC) analysis of epidermal growth factor receptor (EGFR) expression were performed using the methods described in our previous study [9].

Oncological follow-up

These patients were followed up for a median of 24.7 months (range, 5.1–41.3 months). Follow-ups included physical examinations and carcinoembryonic antigen measurements every 3 months for the first 2 years and twice a year thereafter. A computed tomography (CT) scan of the abdomen and thorax was arranged every 3 months for the first 3 years and every 3–6 months thereafter. We performed colonoscopies within 1 year after surgery and held follow-ups at 3-year intervals. Magnetic resonance imaging and positron emission CT were only used when necessary.

Statistical analysis

Data were analyzed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). PFS and OS rates were plotted using the Kaplan–Meier method. PFS was defined as the time from the start date of treatment until the date of any type of progression or the final follow-up, and OS was defined as the time from the beginning of treatment to death from any cause or to the final follow-up. PFS and OS were evaluated using the Kaplan–Meier method, and the log-rank test was used to compare time-to-event distributions. Statistical significance was set at $P < 0.05$.

Results

Patient series, tumor characteristics, and mutation status

In total, 206 patients with single-site mCRC were included in the analysis. Of these, 15 (15/206, 7.3%) patients were subsequently diagnosed as having PC-only CRC, 145 (145/206, 70.4%) were diagnosed as having LiM-only CRC, and 46 (46/206, 22.3%) were diagnosed as having LuM-only CRC. The median age was 65.0 years (range, 37–71 years) in the PC-only group, 62.0 years (range, 26–90 years) in the LiM-only group, and 65.5 years (range, 41–86 years) in the LuM-only group. The status of LiM-only or LuM-only patients was not related to primary tumor location ($P = 0.191$). Moreover, in 109 (75.1%) patients with LiM-only CRC and 33 (71.7%) patients with LuM-only CRC, the primary tumors originated from the left colon. A comparable rate of occurrence from the right or left colon in patients with PC-only CRC was observed; the primary tumors of eight (53.3%) patients with PC-only CRC originated from the left colon.

Genotyping of *KRAS*, *NRAS*, *BRAF*, and EGFR as well as overexpression analysis revealed no significant differences in metastatic site (Table 1). *KRAS* and *NRAS* mutations were evident in respectively 2 patients (16.7%) and 1 (8.3%) patient with PC-only CRC, 39 (36.4%) and 6 (7.3%) patients with LiM-only CRC, and 12 (36.4%) and 2 (7.1%) in patients with LuM-only CRC. *BRAF* and EGFR overexpression was respectively evident in 2 (15.4%) and 12 (92.3%) patients with PC-only CRC, 7 (6.9%) and 76 (89.4%) patients with LiM-only CRC, and 1 patient (2.9%) and 16 (84.2%) patients with LuM-only CRC. FOLFIRI (folinic acid + fluorouracil + irinotecan) plus bevacizumab was the first-line treatment for patients with PC-only CRC, and irinotecan dose escalation was conducted according to *UGT1A1* polymorphism [8, 12].

Survival evaluation

In patients with PC-only CRC, the median PFS was 18.0 months (range, 3.7–38.4 months), and the median OS was 24.6 months (range, 5.1–41.3 months). Among the 15 patients with PC-only CRC, six remained alive at the final follow-up visit conducted in November 2020. During the same period, the PFS of those with LiM-only and LuM-only CRC was 18.2 months and 26.6 months, and the OS of those with LiM-only and LuM-only CRC was 25.0 months and 44.5 months. Patients with PC-only mCRC did not have significantly inferior PFS or OS rates compared with patients with LiM-only or LuM-only mCRC (Figure 2 and 3, both $P > 0.05$).

Discussion

Approximately 20% of patients with CRC had metastases at their initial diagnosis. Furthermore, in almost 40% of the remaining patients, their (initially limited) diseases progressed to metastases during treatment [13]. The tumor cell entrapment hypothesis explained how peritoneal metastases occurred through the shedding, binding, migration, and survival of cancer cells [14]. Peritoneal metastasis is associated with higher risks of death from all causes, and the reported median OS after 5-fluorouracil-only systemic chemotherapy is 5 to 7 months [15–16] and varies between 13 and 34 months, depending on the chemotherapeutic and molecular targeting agents used [17–19]. Because the plasma–peritoneal barrier reduces intraperitoneal drug penetration, systemic chemotherapy for PC-only CRC has only limited efficacy. According to a meta-analysis, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) provided survival benefits for select patients with PC from CRC [20]. A summarized analysis of these 76 studies indicated that the median OS was approximately 29 months in the CRS plus HIPEC group. However, the patients were selected according to their favorable performance status and were able to receive surgical intervention, and the mean mortality and morbidity rates of those in the HIPEC program were 2.8% and 33.0%, respectively. In 2021, Quénet et al. reported both the absence of an OS benefit after the addition of HIPEC to CRS and more frequent late postoperative complications; they suggested that CRS alone should be the cornerstone of therapeutic strategies with curative intent for colorectal peritoneal metastases [21]. In our study, the median PFS and OS rates of 15 PC-only CRC patients given first-line treatment of FOLFIRI plus bevacizumab were 18.0 and 24.6 months, respectively, and irinotecan dose escalation depended on *UGT1A1* polymorphism.

Irinotecan must be converted by a carboxylesterase to SN-38, which is actively cytotoxic and is detoxified by glucuronidation activity of uridine diphosphate glucuronosyltransferase (UGT) ; therefore, the *UGT1A1* genotype represents the development of drug-associated adverse events (AEs). In a genotype-directed dose-determination study on irinotecan dose escalation in patients given first-line FOLFIRI for mCRC, patients with homozygous *UGT1A1**28/*28 developed more severe irinotecan-associated AEs more frequently than did patients with other genotypes [22]. By contrast, the clinical presentations of patients with *UGT1A1**1/*28 exhibited individual variations; however, the recommended initial irinotecan dose of 180 mg/m² was generally well-tolerated in these patients [23]. Conversely, patients with the homozygous *UGT1A1**1/*1 genotype had less severe irinotecan-associated AEs and could tolerate an irinotecan dose as high as 260 mg/m² [24]. Patients with the *UGT1A1**1/*1 and *1/*28 genotypes received high doses of irinotecan to achieve a favorable objective response rate (ORR) without major AEs [25]. According to the pan-Asian-adapted European Society for Medical Oncology (ESMO) consensus guidelines, patients with a favorable *UGT1A1* genotype (homozygous wild *1/*1 and heterozygous *1/*28) can tolerate high-dose irinotecan without notable toxicity [26]. In our research, 12 of the 15 patients with PC-only CRC had the *UGT1A1**1/*1 genotype; three patients with the *UGT1A1**1/*1 genotype received escalated irinotecan doses up to 260 mg/m², and four patients with the *UGT1A1**1/*1 genotype received escalated irinotecan doses up to 210 or 240 mg/m² (Table 2).

In patients with mCRC, the respective 5-year survival rates of those with resectable hepatic, pulmonary, and peritoneal metastases were approximately 60%, 40%, and 20% [27–31], respectively, and peritoneal metastases were associated with a 20% reduction in PFS and a 30% reduction in OS compared with nonperitoneal metastatic mCRC [32]. Our results demonstrated that clinical outcomes were improved by irinotecan dose escalation according to *UGT1A1* polymorphisms in patients with PC-only mCRC treated with first-line bevacizumab and FOLFIRI; the median PFS and OS of patients with PC-only mCRC were 18.0 months and 24.6 months, respectively. Overall, in the present study, patients with PC-only mCRC had comparable PFS and OS to patients with LiM-only or LuM-only CRC. However, ours was only an observational study with a relatively small sample size; future investigations could have a longer follow-up and larger sample sizes to confirm the findings of our study.

Conclusion

Although chemotherapy regimens with new chemotherapeutic and molecular targeting agents improved mCRC outcomes, patients with PC-only mCRC were still considered to have poor clinical outcomes. In summary, our research suggests that patients with PC-only mCRC treated with first-line bevacizumab and FOLFIRI and given irinotecan dose escalation according to *UGT1A1* polymorphism might obtain outcomes comparably favorable to those of patients with LiM-only or LuM-only mCRC. Further prospective randomized trials and comparison studies based on PC status should be conducted, and further research on the molecular and genetic profile may help patients with Pc-only mCRC.

Abbreviations

CRC:colorectal cancer
mCRC:metastatic colorectal cancer
PC: peritoneal carcinomatosis
LIM: liver metastasis
LuM: lung metastasis
OS: overall survival
PFS: progression-free survival
FOLFOX: folinic acid + fluorouracil + oxaliplatin
FOLFIRI: folinic acid + fluorouracil + irinotecan
UGT1A1: uridine diphosphate glucuronosyltransferase 1A1
IHC: immunohistochemical
CT: computed tomography
CRS: cytoreductive surgery
HIPEC: hyperthermic intraperitoneal chemotherapy
UGT: uridine diphosphate glucuronosyltransferase
AEs: adverse events
ORR: objective response rate
ESMO: European Society for Medical Oncology

Declarations

Ethics approval and consent to participate

All aspects of this study were approved by the institutional review board of Kaohsiung Medical University Hospital. Finally, this study was a retrospective review of 206 patients with mCRC, and written informed consent was obtained from all patients (KMUHIRB-E(I)-20200036).

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare no conflict of interest.

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None.

Authors' contributions

C-CL, being the first author of this manuscript, designed this study, analyzed the data, and wrote the manuscript. T-KC, Y-CC, H-LT, C-WH, W-CS, C-JM, T-CY, and P-JC made substantial contributions in terms of the data acquisition, interpretation and statistical analyses, in addition to assisting with the manuscript preparation. J-YW, being the corresponding author for this manuscript, also participated in the study design and coordination, in addition to making critical revisions to the manuscript. All authors have reviewed and approved submission of the final version of the manuscript.

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Tables

Due to technical limitations, table 1 and 2 is only available as a download in the Supplemental Files section.

Figures

Figure 1

CONSORT flow chart for the 398 patients with mCRC; data were collected from Kaohsiung Medical University Hospital cancer center 2014.1.1–2018.12.31).

Figure 2

Kaplan–Meier analysis of progression-free survival in all 206 patients with mCRC. PC-only versus LiM-only versus Lu-only mCRC = 18.0 versus 18.2 versus 26.6 months ($P = 0.194$). mPFS, median progression-free survival

Figure 3

Kaplan–Meier analysis of overall survival in all 206 patients with mCRC. PC-only versus LiM-only versus LuM-only mCRC = 24.6 versus 25.0 versus 44.5 months ($P = 0.191$). mOS, median overall survival

Supplementary Files

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