Prognosis for metastatic colorectal cancer patients achieving complete response after systemic chemotherapy

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Abstract

Purpose: Despite marked recent advances in chemotherapy, few reports have focused on the prognosis for patients with metastatic colorectal cancer (mCRC) achieving complete response (CR) after systemic chemotherapy. This study investigated the clinical course of mCRC patients achieving CR and evaluated the role of CR in chemotherapy.

Methods: This retrospective study searched a prospectively maintained database at the author's institute to identify medical records for mCRC patients achieving CR after systematic chemotherapy from January 2007 to March 2020.

Results: The search yielded 23 patients with confirmed CR to systemic chemotherapy. Median time to CR from treatment initiation was 6.8 months. Maintenance chemotherapy was continued for 22 of 23 patients. Median duration of maintenance chemotherapy was 11.1 months. Disease progression occurred for 17 (73.9%) patients at a median 48.1-month follow-up. Median progression-free survival was 26.6 months. Median overall survival was 91.7 months.

Conclusions: Patients with CR to chemotherapy had a high probability of disease progression, but a relatively long-term prognosis. Treatment strategies after achievement of CR should be based on an understanding of the high potential that tumor cells will remain. Use of maintenance chemotherapy after achievement of CR is still unclear, the recent data do not demonstrate a negative impact for continuing maintenance chemotherapy after CR.

Introduction

In Japan, >137,000 cases of colorectal cancer (CRC) are diagnosed annually; approximately 20% of these patients will have synchronous distant metastasis.[1, 2] An estimated 75–90% of patients with distant metastasis have unresectable lesions.[3] With best supportive care, median survival time (MST) for patients with unresectable CRC is approximately 8 months,[4] and advances in systemic chemotherapy have improved MST to approximately 30 months.[5, 6] Complete response (CR) rate is also improving, although still low. In the 1990s, the backbone of systematic chemotherapy in metastatic colorectal cancer (mCRC) was 5-fluorouracil with leucovorin, which yielded only a <1% CR rate. In the 2000s, standard systemic chemotherapy for mCRC was 5-fluorouracil-based chemotherapy in combination with new cytotoxic drugs, oxaliplatin or irinotecan, which improved the CR rate to 4–6%. Furthermore, a higher CR rate of 8% has been reported for triplet chemotherapy FOLFOXIRI.[7–10] Despite these improvements, few reports have addressed the clinical course of patients achieving CR. This study evaluated the clinical course of mCRC patients achieving CR after systematic chemotherapy and the role of CR in chemotherapy.

Methods

This retrospective study searched a prospectively maintained database at the author's institute to identify medical records for mCRC patients achieving CR after systematic chemotherapy from January 2007 to March 2020. For all patients, the histologic diagnosis was adenocarcinoma of the colon and rectum. The study enrolled only patients achieving CR with systematic chemotherapy, regardless of previous surgery. Exclusion criteria were surgery for curative attempt of residual metastases after systematic chemotherapy and achievement of CR after local chemotherapy (e.g., hepatic arterial infusion chemotherapy.) The study was conducted in accordance with the Declaration of Helsinki.

In the authors' hospital, treatment for mCRC was performed according to the Japanese Society for Cancer of the Colon and Rectum guidelines.[2, 11, 12] After initiation of systemic chemotherapy, tumor response was evaluated using computed tomography scan and magnetic resonance imaging scan every 2–3 months based on response evaluation criteria for solid tumors.

For patients who achieved CR, the management plan was to continue maintenance chemotherapy with a goal of 6–12 months or until disease progression. Patients who continued maintenance chemotherapy without major adverse events and disease progression had the option of continuing of maintenance chemotherapy for >12 months. For patients with disease progression after achievement of CR, resectability of the metastatic lesions was evaluated. If resectable, then curative resection was performed. If unresectable, then systemic chemotherapy was selected.

Statistical Analysis

Statistical calculations were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Survival was calculated with the Kaplan–Meier method.

Results

Patient Characteristics and Systematic Chemotherapy

The search yielded 23 patients with confirmed CR to systemic chemotherapy. All patients had a primary tumor resection before starting systemic chemotherapy. Metastases in only 1 organ were noted for 15 patients (64.9%): 7 were distant lymph nodes (30.3%), 6 liver (26.0%), 1 lung (4.3%), and 1 peritoneum (4.3%).

Metastases in 2 organs were noted for 8 patients (35.1%), and no patients who had metastases lesions in ≥ 3 organs had confirmed CR. Median time to CR from initiation of systemic chemotherapy was 6.8 months (3.0–31.6 months, Fig. 1). With first-line chemotherapy, 20 (87%) patients had confirmed CR; with second-line or later chemotherapy, 3 (13%) had confirmed CR. Table 1 lists characteristics of patients with CR to systematic chemotherapy.

Table 1
Characteristics of patients with complete response to systematic chemotherapy

		All (n = 23)
Age	Median	61
	Range	34–84
Sex	M	13 (56.5%)
	F	10 (43.5%)
Primary lesion site	R	10 (43.5%)
	L	13 (56.5%)
Disease status	Initial diagnosis	12 (52.2%)
	Recurrence	11 (47.8%)
Prior chemotherapy	Yes	2 (8.7%)
	No	21 (91.3%)
Metastatic lesions	Liver only	6 (26.0%)
	Lung only	1 (4.3%)
	distant lymph nodes only	7 (30.4%)
	peritoneum only	1 (4.3%)
	Liver & Lung	2 (8.7%)
	Liver & distant lymph nodes	1 (4.3%)
	Liver & peritoneum	3 (13.0%)
	Lung & distant lymph nodes	2 (8.7%)
	distant lymph nodes & peritoneum	1 (4.3%)
Line	1st	20 (87.0%)
	2nd	2 (8.6%)
	3rd	1 (4.3%)
Regimen	FOLFOX + BEV/PANI/CET	9 (39.1%)
	Xelox + BEV	8 (34.8%)
	FOLFIRI + BEV/PANI/CET	1 (4.3%)
	IRIS + BEV	2 (8.7%)

	All (n = 23)
CPT11 + CET	1 (4.3%)
FOLFOXIRI + BEV	1 (4.3%)
5 FU/LV	1 (4.3%)

Maintenance chemotherapy was continued for 22 of 23 patients; 1 patient had confirmed pathological CR. Disease progression occurred for 11 patients during maintenance chemotherapy, and 2 patients discontinued maintenance chemotherapy in <6 months due to adverse events. Median duration of maintenance chemotherapy was 11.1 months (1.7–36.8 months).

Prognosis For Patients Achieving Cr To Systematic Chemotherapy

Of the 23 patients with CR, 6 (26.1%) maintained CR and 17 (73.9%) had disease progression after a median follow-up of 48.1 months. Curative resection was achieved in 6 of the 17 patients with disease progression; of these 17 patients, 2 have remained disease free; 6 have continued treatment, and 9 had disease progression and died.

Median progression-free survival (PFS) was 26.6 months (95% confidence interval [CI] 17.7–29.6 months, Fig. 2). Median CR duration was 14.7 months (95% CI 8.7–22.9 months). No disease progression was observed in patients who maintained CR for >24.3 months. Median overall survival (OS) was 91.7 months (95% CI 45.7–NA months; Fig. 3).

Discussion

Despite marked recent advances in chemotherapy, few reports have addressed the prognosis for mCRC patients achieving CR. Despite the small sample size, the results of this study are significant for understanding the clinical course of the patients achieving CR. Clinical outcomes were evaluated for 23 CRC patients confirmed CR to systematic chemotherapy. Results showed that patients with CR to chemotherapy had a high probability of disease progression, but a relatively long-term prognosis.

Although CR determined imaging is a useful criterion for evaluating the efficiency of chemotherapy, some liver metastasis studies have reported a discrepancy between CR visualized by imaging versus pathologically confirmed CR. Approximately 20–25% of liver metastases disappear after systemic chemotherapy; among such disappearing liver metastasis (DLM), “true CR” has been reported in 33–83% of cases. Therefore, resection is recommended for DLM after chemotherapy.[13–16] In the present study, 17 (73.9%) patients with CR to systematic chemotherapy had disease progression after a median follow-up duration of 48.1 months. Another study also reported that 84% of patients with CR had disease

progression.[8] These data indicate a discrepancy between CR determined by imaging and actual complete clearance of cancer in other organs.

Use of maintenance chemotherapy after achievement of CR is unclear. Research has shown negative results for maintenance chemotherapy after achievement of CR. Dy GK et al compared OS in 22 of 62 patients with CR with <2 cycles of maintenance chemotherapy and 40 patients with >2 cycles of chemotherapy in 2007. As a result, OS from CR was 39.8 months and 29.2 months, respectively; maintenance chemotherapy did not prolong OS.[8] However, the therapeutic background for the 2007 study differs from the present context. Treatment strategies after achievement of CR have not been established; the approach should be based on the high potential for tumor cells to remain even after CR. Furthermore, the OPTIMOX2 study, which compared chemotherapy discontinuation with maintenance therapy, indicated that planned complete discontinuation of chemotherapy had a negative impact on duration of disease control and PFS versus the maintenance therapy strategy.[17] Therefore, in the present study, maintenance chemotherapy was continued until disease progression or for 6–12 months after CR, except for cases in which pathological CR was confirmed after surgery for DLM. Median duration of maintenance chemotherapy was 11.1 months.

In the present study, median PFS was 26.6 months and median OS was 91.7 months, which exceeds the PFS (15.4 months) and OS (44.3 months) in the 2007 study.[8] These more recent findings indicate that advances in chemotherapy have improved the prognosis of patients with CR; however, direct comparison with the 2007 study is difficult results because of different therapeutic backgrounds, and the recent data do not demonstrate a negative impact for continuing maintenance chemotherapy after CR.

This study has some limitations. First, a relatively small patient sample was derived from a single institution. Second, systematic chemotherapy regimens were not uniformly introduced, which result in treatment bias.

Conclusions

Although CR by imaging is a useful criterion for evaluating efficiency of chemotherapy, it does not mean actual complete clearance of cancer. Treatment strategies after the achievement of CR should be decided based on the understanding of a high possibility that tumor cells will remain even if the patient has achieved CR.

Abbreviations

CR, complete response; CRC, colorectal cancer; DLM, disappearing liver metastasis; JSCCR, Japanese Society for Cancer of the Colon and Rectum; MCIJ, monitoring of cancer incidence in Japan; MST, median survival time; OS, overall survival; PFS, progression-free survival

Declarations

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Competing interests

The authors declare that they have no conflicts of interest.

Authors' contributions

Takahiro Manabe wrote the initial draft of the manuscript. Yasumasa Takii was involved in the preparation of the manuscript. All other authors critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The study procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this studies before study inclusion.

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Figures

Figure 1

Time to complete response from initiation of systemic chemotherapy

Figure 2

Progression-free survival

Figure 3

Overall survival