Evaluating the recent developments in palliative chemotherapy for metastatic colorectal cancer

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The incidence of colorectal cancer (CRC) has increased. CRC is the third most common cancer and the fourth most common cause of cancer-related deaths in Korea. Palliative chemotherapy can be used to shrink tumors and ease symptoms caused by the cancer when cure is not possible. It is important to identify chemotherapeutic agents that can be used to effectively treat metastatic CRC (mCRC) and thus improve the survival and quality of life of patients with mCRC. This review aimed to evaluate the recent developments in palliative chemotherapy for mCRC and the biological or targeted agents used based on genetic alterations.

Keywords: Palliative; Chemothreapy; Metastatic colorectal cancer; Survival

INTRODUCTION

In Korea, colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer-related deaths [1]. Stage IV CRC accounted for 15% to 20% [2] and about 20% to 30% of cases of advanced relapsed CRC [3,4]. Effective therapeutic combinations can improve the survival and increase the rate of curative intent resections for metastatic CRC (mCRC). Patients with unresectable mCRC should be offered palliative chemotherapy. Cytotoxic chemotherapy of mCRC uses a combination of cytotoxic agents such as fluorouracil (FU), leucovorin (LV), capecitabine, irinotecan, and oxaliplatin for chemotherapy. Depending on whether cancer has RAS mutation (RAS-mt), biologic agents such as angiogenesis-targeting and epidermal growth factor receptor (EGFR)-targeting agents can be used as cytotoxic agents for combination chemotherapy. Recently, other molecular driver mutations such as BRAF (V600E) mutation (BRAF-mt), and human epidermal growth factor receptor 2 (HER2) amplification have led to the development of novel therapeutic targets. BRAF inhibitors, mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitor, EGFR targeting drug, and HER2-targeting drug have been recently developed after recognizing molecular driver mutations. In
2017, the U.S. Food and Drug Administration approved pembrolizumab and nivolumab for microsatellite instability-high (MSI-H) or mismatch repair-deficient CRC that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. This review aimed to evaluate the recent developments in palliative chemotherapy for mCRC and the agents used based on genetic alterations.

**COMBINATION WITH BIOLOGIC AGENTS**

**Angiogenesis-targeting agents**

Bevacizumab, a vascular endothelial growth factor A (VEGF-A) targeting monoclonal antibody, has been approved as first-line therapy for mCRC based on randomized phase III trial (AVF2107) in 2004. This trial compared irinotecan, 5FU, and LV (IFL) with IFL plus bevacizumab, which showed superior RR, PFS, and overall survival (OS) [17]. Although a few trials failed to show the advantage of bevacizumab [18,19], some subsequent phase III trials demonstrated benefit of PFS or RR when bevacizumab was combined with first-line cytotoxic chemotherapy agents such as XELOX, FOLFOX, or capecitabine [20-22]. Bevacizumab also improved PFS and RR when combined with 5FU triplet, 5-FOLFOXIRI compared with bevacizumab plus FOLFIRI [23].

The addition of bevacizumab, as biologic agent, to XELOX, FOLFOX, FOLFIRI, or FOLFOXIRI was the recommended first-line chemotherapy for mCRC. Anti-VEGF therapy as second-line chemotherapy included addition or continuation of bevacizumab or combination of another anti-angiogenic agent with cytotoxic chemotherapy. Giantonio et al. [24] have demonstrated the advantage of OS, PFS, and RR from the addition of bevacizumab to FOLFOX in bevacizumab-naïve mCRC patients as second-line chemotherapy. The ML18147 study proved the survival benefit of continuing bevacizumab in patients who had progressed after first-line bevacizumab plus combination chemotherapy [25]. Aflibercept, a VEGF-a/b and placenta growth factor (PGF)-binding fusion protein, in combination with FOLFIRI in patients with mCRC who had progressed on first-line oxaliplatin-fluoropyrimidine therapy has resulted in modest improvement in PFS and OS compared with FOLFIRI plus placebo [26]. Ramucirumab, a VEGFR2 targeting monoclonal antibody, in combination with FOLFIRI for patients with mCRC who had progressed after first-line therapy with bevacizumab and oxaliplatin, has also resulted in improvements in PFS and OS [27].

If the patient’s disease progresses after receiving first-line chemotherapy, bevacizumab plus alternative combination chemotherapy could be used as second-line therapy. In cases where patients progresses after receiving first-line oxaliplatin-based therapy, they could be considered for aflibercept or ramucirumab plus FOLFI-
RI treatment.

Regorafenib, an oral multi-kinase inhibitor that blocks the activity of several protein kinases including VEGFR1/2/3, platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR), has been proven effective against mCRC that had progressed after standard therapies by improving OS of patients [28].

Regorafenib monotherapy would be one of the options for mCRC patients after standard therapies.

EGFR-targeting agents

Several studies evaluating the effectiveness of EGFR-targeting drugs comprising cetuximab and panitumumab involved molecular studies to identify biomarkers. Although RAS-mt has been known as a biomarker of EGFR-targeting drugs, initial trials of cetuximab enrolled patients with immunohistochemically detectable EGFR expression. The NCI-CO17 study confirmed the efficacy of cetuximab as the best supportive care for chemotherapy-resistant mCRC and demonstrated that KRAS exon 2 mutation was a negative predictive biomarker [29,30]. Molecular analysis in subsequent clinical trials demonstrated that patients with KRAS exon 2 or other RAS-mt did not benefit from the addition of cetuximab or panitumumab [31-33]. RAS-mt occurs in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146). Mutations in KRAS exon 2 codons account for about 86% of KRAS variants and about 42% of mCRC. Mutations in KRAS exons 3 and 4 and NRAS exons 2, 3, and 4 account for around 10% of mCRC cases [34].

Two early clinical trials at first-line setting of mCRC doubted the efficacy of cetuximab in combination with oxaliplatin-based chemotherapy [35,36]. The COIN study used FOLFOX or XELOX according to the physician’s choice. Adding cetuximab to these regimens remained unbeneﬁcial [35]. The addition of cetuximab to XELOX resulted in the reduction of dose intensity and increase in capecitabine toxicities. However, FOLFOX with cetuximab improved PFS compared with FOLFOX in subgroup analysis. The CRYSTAL study investigated the addition of cetuximab to FOLFIRI. Addition of cetuximab improved the RR, PFS, and OS [37,38]. Panitumumab, a fully human immunoglobulin G2 antibody, in combination with FOLFLOX chemotherapy in KRAS wild-type patients showed efficacy in improving PFS [39].

Cetuximab and panitumumab with FOLFOX or FOLFIRI can be used as first-line chemotherapy in mCRC patients with RAS wild type. In addition, cetuximab could be considered in combination with irinotecan in patients with irinotecan-refractory CRC.

Selection of biologic agent in RAS wild type

Which among the biologic agents (bevacizumab and cetuximab or panitumumab) are more effective against RAS wild type? Three studies have been conducted to address this question. However, the superiority of either bevacizumab or cetuximab/panitumumab has not been established yet. A randomized phase III study, FIRE-3 (n = 592), compared cetuximab and bevacizumab in combination with FOLFIRI chemotherapy in patients with KRAS wild type. It found no significant difference in RR as primary endpoint [40]. A randomized phase II study, the PEAK (n = 289), compared the effectiveness of panitumumab and bevacizumab in combination with FOLFOX chemotherapy in mCRC patients with KRAS wild type. It found no significant difference in PFS as primary endpoint [41]. A randomized phase III study, CALGB/SWOG 80405 trial (n = 1,137), also involved mCRC patients with KRAS wild type. Results showed that there was no significant difference in OS as primary endpoint between patients treated with cetuximab and those treated with bevacizumab combined with mFOLFOX6 or FOLFIRI as first-line therapy [42]. Although the FIRE-3 study and PEAK study reported OS benefit in cetuximab or panitumumab group, no significant difference in OS, PFS, or RR was observed among these groups in the CALGB/SWOG 80405 trial, the largest among the three trials, which enrolled 1,000 patients.

Either anti-angiogenic agent such as bevacizumab or anti-EGFR inhibitors including cetuximab or panitumumab with FOLFOX/XELOX or FOLFIRI would be recommended as the first-line chemotherapy in mCRC patients with RAS wild type.

In addition, the CALGB/SWOG 80405 trial suggested that the primary tumor location might be a predictive biomarker as well as a prognostic biomarker in patients with KRAS wild type. A meta-analysis of first-line therapy for RAS wild type demonstrated that patients with left side colon cancer had a significant survival benefit.
from anti-EGFR agents than with anti-VEGF agent added to standard chemotherapy [43,44].

In left side colon cancer with RAS wild type, anti-EGFR inhibitors are preferred as biologic agents combined with FOLFOX/XELOX or FOLFIRI as first-line chemotherapy.

**THERAPEUTIC GOALS**

**Potentially resectable liver metastatic disease**
The 5-year survival rate of patients with mCRC and liver metastasis that underwent metastasectomy and primary lesion resection was 35% to 60% [45]. A previous prospective randomized trial proved the benefit of adjuvant FL chemotherapy following R0 hepatic metastasectomy [46]. A pooled analysis showed the same result [47]. The EORTC 40983 study compared perioperative chemotherapy with FOLFOX4 and surgery and surgery alone for resectable liver metastases from mCRC [48]. This study proved that FOLFOX as perioperative chemotherapy effectively reduced the risk of adverse events that could affect PFS. However, the addition of anti-EGFR antibody to FOLFOX in these patients did not improve the outcomes [48]. Whether surgery should be performed first or the exact number of cycles of preoperative chemotherapy remains unclear. Prolonged preoperative chemotherapy could increase the risk of postoperative complications after major liver resection as it is associated with liver problems such as fatty liver, steatohepatitis, or sinusoidal injury due to cytotoxic chemotherapy [49]. Karoui et al. [50] reported that morbidity in the chemotherapy group increased among patients receiving six or more cycles of chemotherapy.

Primary lesion resection and metastasectomy with perioperative chemotherapy should be considered in mCRC patients with potentially resectable liver metastasis. However, the effect of using a combination of biologic agents remains unclear.

**Unresectable disease**
Some prospective studies have reported the downsizing of patients with colorectal liver metastases for rescue surgery following combination chemotherapy, with R0 resection of 20% to 50% and median OS of 17 to 48.8 months [51]. Conversion chemotherapy administered in patients with initially unresectable liver metastasis increased the resectability of liver metastasis and improved their survival [52]. The combination of either oxaliplatin- or irinotecan-based chemotherapy and EGFR antibody for RAS-wild type or anti-VEGF antibody can improve Ro resection rates [53,54]. FOLFOXIRI with bevacizumab can improve tumor RR, resection rate, and PFS than FOLFOX with bevacizumab [51].

Effective conversion chemotherapy and resection of primary lesion and liver metastasis could improve the outcome of mCRC patients with unresectable liver metastasis. The use of a combination of cytotoxic chemotherapy and biologic agents as doublet or bevacizumab plus FU, LV, and oxaliplatin are recommended to convert the unresectable tumor to resectable tumor.

**Optimization of chemotherapy**

**Subsequence therapy**
For mCRC patients with RAS wild type who were treated with anti-angiogenic agent such as bevacizumab or anti-EGFR inhibitor including cetuximab or panitumumab plus FOLFOX/XELOX or FOLFIRI or bevacizumab plus FOLFOXIRI as first-line chemotherapy and vice versa, cytotoxic agents could be considered. Cytotoxic agents with two sequences of FOLFOX/XELOX followed FOLFIRI and vice versa showed similar efficacy [10]. If FOLFOX/XELOX plus bevacizumab was used as the first-line chemotherapy, FOLFIRI plus bevacizumab, ramucirumab, or aflibercept could be considered as the second-line chemotherapy. If FOLFIRI plus cetuximab or panitumumab was used as the first-line chemotherapy, FOLFOX/XELOX plus cetuximab or panitumumab was used as the first-line chemotherapy, if patients who were resistant to irinotecan did not receive cetuximab previously, they could be considered for cetuximab plus irinotecan therapy.

In mCRC patients with RAS mutant type, bevacizumab with FOLFOX/XELOX, FOLFIRI, or FOLFOXIRI could be used because of no efficacy of anti EGFR inhibitors. If FOLFOX/XELOX plus bevacizumab was used as the first-chemotherapy, FOLFIRI plus bevacizumab, ramucirumab, or aflibercept could be considered as the sec-
ond-line chemotherapy. If FOLFIRI plus bevacizumab was used as the first-line chemotherapy, FOLFOX plus bevacizumab could be considered as the second-line chemotherapy.

Regardless of RAS-mt status, regorafenib or TAS 102 could be considered in patients with mCRC who are resistant to oxaliplatin and irinotecan.

Continuous or intermittent therapy
The optimal duration of palliative chemotherapy for unresectable disease that does not progress remains controversial. Oxaliplatin causes cumulative neurotoxicity, which generally induces discontinuation of chemotherapy. OTIMOX1 study has investigated whether continuous therapy provides better outcomes than intermittent therapy to achieve better response after chemotherapy. In this study, 620 previously untreated patients were randomly assigned to FOLFOX4 every 2 weeks until progression (arm A), or FOLFOX7 for 6 cycles only, followed by reinduction of oxaliplatin at the time of progression after 12 cycles of non-oxaliplatin-containing regimen (arm B). Median survival was similar between the two groups. However, patients in arm B had lower risk of grade 3/4 toxicity during cycles 6 to 18 [55].

Considering the increased toxicities due to continuous treatment, intermittent therapy could be used as an alternative treatment.

Maintenance therapy
The efficacy of bevacizumab alone or bevacizumab with FL or capecitabine combined with FOLFOX/XELOX was investigated. CAIRO 3 study was conducted to determine the efficacy of capecitabine plus bevacizumab in patients with stable disease or evaluate the results after six cycles of XELOX plus bevacizumab. The maintenance therapy group showed longer PFS [56]. Comparing treatment break and continuation of bevacizumab alone, the continuous administration of fluoropyrimidine and bevacizumab until progression after first-line combination therapy improved patients’ PFS [57].

Administering maintenance therapy with 5-FU and bevacizumab after first-line FOLFOX/XELOX with bevacizumab was found to be effective.

SPECIAL CONSIDERATIONS

Other chromosomal instability
BRAF-mt and HER2 amplifications account for about 5% and 3% of mCRC, respectively. Because RAS-mt, BRAF-mt, and HER2 amplifications are mutually exclusive [35,58], in patients with RAS wild-type disease, the rate of BRAF-mt or HER2 amplification increased. Use of BRAF inhibitors and HER2-targeting drugs improved the outcomes of patients with mCRC.

BRAF-mt is more prevalent in patients with proximal colon tumors. It has unique pathologic features such as poorer differentiation, mucinous histology, and MSI [59]. BRAF-mt confers worse prognosis in metastatic setting. However, it does not predict response to standard chemotherapy. The predictive value of anti-EGFR antibodies for patients with BRAF-mt remains controversial. However, results suggested that patients with BRAF-mt might not benefit from cetuximab or panitumumab. The European Society for Medical Oncology (ESMO) guideline recommend triplet chemotherapy combined with bevacizumab to manage aggressive BRAF-mt mCRC in fit patients [60].

BRAF, a modulator of the MAPK pathway, has recently emerged as a promising new target for the treatment of CRC. Monotherapy using BRAF inhibitors has a poor RR (5%) [61]. This primary resistance results from feedback signals that can reactivate MAPK signaling. To overcome this resistance, BRAF inhibitors have been studied in combination with inhibitors of MARK pathway mediators. Dual inhibition of BRAF and MEK such as in BRAF-mt melanoma, dual inhibition of EGFR and BRAF with or without irinotecan, or use of triple combination therapy has been studied with promising data [59].

Although the incidence of HER2 amplification of mCRC is known to be below 5%, in patients with both RAS and BRAF wild-type diseases, a HER2 amplification rate of 14% has been reported [62]. Amplification of the HER gene or overexpression of its protein product has been successfully treated in patients with other types of cancer, most notably breast cancer and gastric adenocarcinomas. HER2 target agents including trastuzumab, lapatinib, and pertuzumab have become important treatment options for these cancers. The HERACLES study demonstrated the efficacy of a com-
Combination of trastuzumab and lapatinib in patients with HER2-positive mCRC who were resistance to standard therapy [63].

Microsatellite instability
MSI is the molecular fingerprint of a deficient mismatch repair system. Approximately 15% of CRC cases display MSI owing either to epigenetic silencing of mutL homolog 1 (MLH1) or germline mutation in one of mismatch-repair (MMR) genes: MLH1, MSH2, MSH6, or PMS2. MSI is diagnosed on the basis of the variable length of DNA microsatellites. It allows mutations to be accumulated at many times and facilitates MSI neoplastic progression. PD-1 inhibitor in MSI-H or mismatch repair-deficient mCRC has demonstrated clinical benefit [64]. Nivolumab has demonstrated efficacy in CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, showing clinical benefit [65].

Most patients with mCRC are mismatch repair proficient and microsatellite stable. Immune checkpoint inhibitors have yet to show clinical activity in these patients. Immune checkpoint inhibitors combined with synergistic drugs such as MEK inhibitors have been tried in these patients to improve tumor immune recognition or promote immune cell accumulation [66].

CONCLUSIONS
New development of chemotherapeautic agent and targeted agents including anti-angiogenic agents or anti EGFR inhibitors and appropriate surgical treatment have improved the prognosis of mCRC. Recently, research on target agents such as BRAF, HER2, MSI-H, and new targeted agents for other abnormalities have been investigated with proven efficacy.

Conflict of interest
No potential conflict of interest relevant to this article was reported.

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