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Conventional and Targeted Therapy in Metastatic Colorectal Cancer

Sedef AM[1] and Sümbül AT[2]*

[1]Departmant of Medical Oncology, Sanliurfa Training and Research Hospital, Turkey

[2]Departmant of Medical Oncology, Baskent University, Turkey

***Corresponding author:** Ahmet Taner Sümbül, Department of Medical Oncology, Faculty of Medicine, Baskent University, Turkey

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Abstract

Colorectal cancer is one of the leading causes of cancer related mortalities and its dismal prognosis is well known. 20% to 25% of colorectal cancer patients have advanced stage disease and systemic chemotherapy is the main treatment for these patients for palliation. But there is a novel treatment option for metastatic colorectal patients. With these novel options median survivals have prolonged from 12 months to nearly 40 months. In this review, we discussed the conventional treatments and new therapy approaches for metastatic colorectal cancer patients.

Keywords: Colorectal cancer; Conventional; Targeted therapies

Introduction

Colorectal cancer is the second leading cause of death in the United States among all cancers [1]. Approximately 20% to 25% of colorectal cancer patients are diagnosed with liver metastasis at the time of initial diagnosis and a further 40% to 50% of patients will develop liver metastasis within 3 years from initial diagnosis [2,3]. Metastatic colorectal cancer is generally not curable disease. However, a subset of patients with isolated metastases to liver and/or lung is potentially curable with local therapies such as surgery. Treatment is systemic chemotherapy with purpose palliation and control of symptoms, control of tumor growth for patients with non-curable metastatic colorectal cancer. The median survival is 5 to 6 months for metastatic colorectal cancer patients without specific therapy. After fluorouracil plus leucovorin (LV) therapy median survival is approximately 1 year for these patients. The addition of oxaliplatin and irinotecan to the fluorouracil and LV therapy provided an improvement in median survival to nearly 20 months since the year 2000. Finally new pathways have been defined and new therapies started to use which targeted these new pathways. Overall survival was increased with these novel agents such as bevacizumab, cetuximab, panitumumab, other TKİs and immunotherapies [4].

Systemic chemotherapy options

Fluorouracil and leucovorin: Fluorouracil (5-FU) has been wildly used as a primary medication in the treatment of solid tumors including colorectal cancer. Although 5-fluorouracil (5-FU) has been used to treat advanced colorectal cancer for 45 years, the drug has only a modest response rate and impact on survival. Until 2000, standard first-line therapy for metastatic colon cancer was the fluoropyrimidine based therapies. This treatment consisted of fluorouracil (FU) and leucovorin. Fluorouracil is a cytotoxic agent which effects by inhibition of DNA and RNA synthesis [5]. Leucovorin (LV) is biomodulator and activator for fluorouracil with inhibition of the enzyme thymidylate synthase and Leucovorin enhances FU cytotoxicity by interacting with thymidylate synthase. Response rates of this combination are in the range of 15% to 25% and compared to FU alone, FU/LV is associated with a twofold higher response rate (21 *vs.* 11 percent) in two meta analyses [6,7], These drugs has been given in various schema and doses such as the Mayo Clinic regimen(425 mg/m^2 of fluorouracil and 20 mg/m^2 for LV on days 1 to 5 every 4 to 5 weeks) and The Roswell Park regimen (500 mg/m^2 of fluorouracil and 500 mg/m^2 of LV administered weekly for 6 out of 8 weeks) [8,9]. Studies comparing different methods of 5-FU administration (bolus injection *vs.* prolonged infusion) have demonstrated improved response rates and decreased toxicity with prolonged infusion, but most have failed to demonstrate statistically significant improvements in survival

Capecitabine: Capecitabine is an oral fluoropyrimidine agent. It is precursor of fluorouracil and metabolized to active form after enzymatic reactions in the liver. The efficacy of capecitabine is similar to FU/LV combinations. Oral capecitabine monotherapy has been shown to have superior antitumor activity to bolus fluorouracil with leucovorin (Mayo Clinic regimen) in this setting, with higher response rates (26% *vs.* 17%, p<0.0002) and at least equivalent TTP and OS in two large randomized studies [10]. The approved dose is 1250 mg/m twice daily for 14 of every 21 days. In animal model experiments, a higher therapeutic index (ratio of the 50% toxic dose and the 50% effective dose) compared to other fluoropyrimidine agents has been reported [11], suggesting that less dosage may still maintain good efficacy with a less toxic profile. Most common side effects are diarrhea and hand-foot syndrome. Capecitabine has been used with combination regimens with both oxaliplatin and irinotecan in metastatic colorectal cancer patients. Other oral fluoropyrimidines are tegafur-uracil, S1 (a prodrug of 5-FU), gimeracil and oteracil.

Irinotecan: Irinotecan is an anti-cancer drug by inhibition of topoisomerase I in metastatic colorectal cancer. It is active as monotherapy but combination with FU is more active than monotherapy. In several clinical studies showed that significant single-agent activity in colorectal cancer resistant to FU-based first-line therapy Firstly, clinical benefit of irinotecan has demonstrated after FU failure in patients with metastatic colorectal cancer with 15% response rates [12-14]. Two first-line phase III trials [15,16] showed a significant improvement in results with the addition of irinotecan to FU-LV combinations therapy (FOLFIRI) Following trials has demonstrated that the role of irinotecan in the first-line

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Table 1: Summary of the treatment of metastatic colorectal patients.

Metastatic Colorectal Cancer with Unresectable metastases										
Molecular testing										
	Any RAS mut (%55)		All RAS wt (% 40)				BRAF mut (%5-10)			
First line	CT doublet/triplet +bevacisumab		CT doublet/triplet +bevacisumab		CT doublet+EGFRinhibitor		FOLFOXIRI+ bevacisumab			
Second line	CT doublet+VEGF inhibitor		CT doublet+VEGF inhibitor		CT doublet+Bevacisumab		EGFR inhibitör?+Chemotherapy			
Third line	Regorofanibe	TAS-102	EGFR inhibitör+irinotecan		Regorafanib	TAS-102	Regorafanib	TAS-102		
Fourth line	BSC		Regorafanib	TAS-102	BSC		BSC			
			BSC							

treatment. One year survival (36 versus 14 percent) and quality of life was superior with irinotecan combinations [13]. Different schedules have similar therapeutic outcomes. Most using schedule is FOLFIRI regimen. The most common side effects of irinotecan are diarrhea, myelosuppression, and alopecia.

Oxaliplatin: Oxaliplatin, a new cytotoxic agent from the diaminocyclohexane platinum family, has a mechanism of action similar to the other platinum derivates, with a different spectrum of antitumor activity against some tumor models; in particular, activity against colon cell lines and synergistic activity of oxaliplatin and FU in experimental models have been demonstrated. Oxaliplatin has limited activity as a single agent, but it shows enhanced efficacy of fluoropyrimidines. In three studies, combinations of oxaliplatin and FU/LV (FOLFOX) had higher antitumor activity compared to FU/LV regimen [17-19]. In first line therapy, a European randomized phase III trial [17] demonstrated significant superiority of the combinations regimen of Oxaliplatin, LV, and bolus plus infusional FU (FOLFOX4) over the Mayo Clinic regimen in terms of response rate (50% *vs.* 22%, respectively; P: 0.0001) and progression-free survival (8.2 *vs.* 6.0 months, respectively; p: 0.0003), with no statistical difference in median OS time (16.2 *vs.* 14.7 months, respectively; p: 0.12). The dose limiting toxicity of oxaliplatin is neurotoxicity. Nausea and vomiting, minimal myelotoxicity are other side effects.

Comparing irinotecan- and oxaliplatin: The outcomes of first line oxaliplatin/FU/LV and irinotecan/FU/LV are similar in head to head comparisons. In the pivotal Intergroup N9741phase 3 trial demonstrated the superiority of FOLFOX compared with IFL as first-line therapy for colorectal cancer. Response rate (45% *vs.* 31%, p=0.002), PFS (8.7 months *vs.* 6.9 months, p=0.0014), and overall survival (19.5 months *vs.* 15.0 months, p=0.0001) were superior with oxaliplatin regimens in this trial [20]. However, in two European trials and a Japanese trial, FOLFOX and FOLFIRI had similar efficacy [21-23]. Combinations of 5-FU/LV, irinotecan, and oxaliplatin (FOLFOXIRI) show high activity but also increased toxicity [24].

Inhibitors of the VEGF System

Angiogenesis is one of the essential causes of tumor progression. The VEGF/VEGF receptor pathway, in particular, contributes to several processes in tumor angiogenesis and inhibition of VEGF is important in metastatic colorectal cancer treatment. The agents targeting VEGF are bevacizumab, aflibercept and ramucirumab. Bevacizumab improves outcomes in first line and next step of treatment. But aflibercept and ramucirumab can use after first line treatment in metastatic colorectal cancer.

Bevacizumab: Bevacizumab is a humanized monoclonal antibody targeting VEGF and it has demonstrated clinical efficacy for the treatment of metastatic colorectal cancer in combination with fluorouracil and LV alone or with irinotecan/oxaliplatin [25-28]. But bevacizumab do not have significant single-agent activity in metastatic colorectal cancer [25]. In a randomised trial addition of bevacizumab was associated with a significant 19 percent reduction in the risk of death, but this translated into a median overall survival advantage of only two months (19.8 *vs.* 17.6 months) and median progression free survival was two months (9.1 *vs.* 6.9 months) [29]. The comparison of IFL with or without bevacizumab was made in a trial of 813 patients. The outcomes of this trial showed the benefit of addition bevacizumab in objective response rate (45 *vs.* 35 percent),time to tumor progression (11 *vs.* 6 months) and median survival (20 *vs.* 16 months) [30]. The benefit of adding bevacizumab to a first line oxaliplatin based regimens is demonstrated in the TREE-2, ECOG 3200 and NO 16966 trials [31-33]. On the other hand, in the phase III ITACa randomized trial, there was no benefit for PFS and overall survival for the addition of bevacizumab to FOLFOX4 [34]. Bevacizumab also adds benefit to first line FU/LV and capecitabine [35,36]. Bevacizumab has serious and potentially fatal adverse effects such as proteinuria, hypertension, bleeding, GI tract perforation, arterial and possibly venous thromboembolic events [37]. Other rare side effects include reversible posterior leukoencephalopathy, nasal septum perforation, and jaw osteonecrosis.

Aflibercept: Intravenous aflibercept is a recombinant fusion protein consisting of human VEGF receptors 1 and 2. The FDA approved aflibercept in 2012 as a component of second-line therapy in combination with FOLFIRI. VELOUR trial showed that aflibercept was benefit for second line treatment after progression of oxaliplatin and bevecizumab based regimen and aflibercept had used with FOLFIRI in this trial. Median overall survival was significantly longer in patients treated with aflibercept (13.5 *vs.* 12.1 months) and median PFS was longer (6.9 *vs.* 4.7 months) [38]. The side effect of aflibercept is similar with bevacizumab.

Ramucirumab: Ramucirumab is a recombinant monoclonal antibody that binds to the VEGFR2. The FDA approved ramucirumab in 2015 as a component of second-line therapy in combination with FOLFIRI. The efficacy of ramucirumab for second line treatment of mCRC was studied in the phase III RAISE trial. In this trial the addition of ramucirumab to FOLFIRI as second line treatment for patients pretreated with a FOLFOX and bevacizumab improved overall survival (median overall survival 13.3 *vs.* 11.7 months; p=0.022) and PFS (5.7 *vs.* 4.5 months) [39]. Grade 3 or worse side

effects with ramucirumab included neutropenia (38 *vs.* 23 percent), hypertension (11 *vs.* 3 percent), and fatigue in this trial.

Agents Targeting the EGFR

The Epidermal Growth Factor Receptor (EGFR) is a transmembrane glycoprotein receptor. EGFR may be involved in autocrine or paracrine control of colorectal cancer (CRC) cell growth, or in the development of angiogenesis or metastases [40,41]. Two monoclonal antibodies (MoAbs) targeting the EGFR are active for treatment of metastatic CRC (mCRC), cetuximab and panitumumab. Cetuximab is a chimeric IgG1 monoclonal antibody that binds to the extracellular domain of the EGFR. Panitumumab is a fully human IgG2 monoclonal antibody that also targets the EGFR. They have single-agent efficacy in advanced colorectal cancer and both cetuximab and panitumumab are only effective in the subset of patients whose tumors have wild type (WT) and not mutated RAS (NRAS, KRAS) oncogenes. Also Anti-EGFR monoclonal antibodies are not beneficial with BRAF mutated patients.

Cetuximab: The single-agent response rate of cetuximab is 10% [42]. Cetuximab is useful in combination with irinotecan for patients with WT RAS tumors. The EPIC trial among oxaliplatin refractory patients showed that addition of cetuximab to irinotecan improved outcomes [43]. In this trial, PFS was significantly higher with combined therapy (median 4 *vs.* 2.6 months) and objective response rates (16 *vs.* 4 percent). But median survival was not significantly different with combination therapy (10.7 versus 10 months). The BOND trial compared irinotecan plus weekly cetuximab versus cetuximab alone in 329 patients with irinotecan refractory mCRC [44]. Combined therapy was associated with a significantly better response rate (23 versus 11 percent) and TTP (4.1 versus 1.5 months). But there was no significantly difference about median survival (8.6 versus 6.9 months). The first line setting of cetuximab was evaluated in the CRYSTAL trial. 1198 patients with previously untreated mCRC were randomly assigned to FOLFIRI with or without cetuximab [45]. Median PFS was significantly better with cetuximab (8.9 *vs.* 8 months) and overall response rate was better with cetuximab (47 *vs.* 39 percent). But there was no significant overall survival benefit with cetuximab. However, among patients with WT KRAS; response rates, median PFS and overall survival were significantly higher with cetuximab arm [46]. The OPUS trial compared weekly cetuximab plus FOLFOX4 versus FOLFOX 4 alone [47]. Cetuximab with oxaliplatin was associated with a significantly higher response rate (57 versus 34 percent) but there was no significant overall survival benefit with combinations therapy. Both OPUS and CRYSTAL trials, patients receiving cetuximab had significantly higher rates of surgery for metastases and higher rates of complete (R0) resection. The COIN and NORDIC VII trials showed that no benefit for adding cetuximab to a first line Oxaliplatin regimen in patients with KRAS wild type tumors [48,49].

Panitumumab: The single-agent response rate of panitumumab was 10 percent in a multicenter trial [50]. Panitumumab has efficacy of first, second, and third line panitumumab in combination with oxaliplatin or irinotecan based regimens in patients with WT RAS tumors [51,52]. In the phase III PRIME trial, There was progression free survival benefit for FOLFOX plus panitumumab regimen (median PFS 9.6 versus 8 months) [53]. In the US by FDA panitumumab is indicated as a first line therapy in combination with FOLFOX, but not with irinotecan containing regimens.

The main toxicities of anti-EGFR antibodies are skin rash, hypomagnesemia, diarrhea, and hypersensitivity reactions, which is particularly relevant for the chimeric antibody cetuximab [54]. The risk of infusion reactions with panitumumab is lower than with cetuximab.

Comparison of EGFR Monoclonal Antibodies and Bevacizumab

EGFR antibodies and bevacizumab should not be combined in first-line therapy. EGFR targeted therapies and bevacizumab compared directly with three trials. These trials are FIRE, PEAK and CALGB/South-west Oncology Group (SWOG) 80405.

The FIRE-3 trial compared the FOLFIRI plus cetuximab or FOLFIRI plus bevacizumab in 592 patients with KRAS exon 2 wild-type colorectal cancer [55]. Median progression free survival (PFS) was similar (10.0 *vs.* 10.3 months) and median overall survival was significantly longer with cetuximab (28.7 *vs.* 25 months) patients The patients who had WT RAS status in KRAS exons 2, 3 and 4 and NRAS exons 2 and 3 had an even more pronounced survival benefit from cetuximab (median overall survival 33.1 *vs.* 25.9 months).

The PEAK trial compared the FOLFOX plus panitumumab or bevacizumab [56]. In the patients with exon 2 WT KRAS, PFS was similar, but median overall survival was significantly better (34 *vs.* 24 months).When the analysis was expanded to include patients who were WT in exons 2, 3, and 4 of KRAS and NRAS, panitumumab was associated with a significant improvement in PFS (median 41 versus 29 months).

In the CALGB/SWOG 80405 trial patients were randomly assigned to receiving cetuximab or bevacizumab with either FOLFOX or FOLFIRI [57]. In a preliminary report at the 2014 ASCO annual meeting, overall survival from was similar (29.9 months for cetuximab and 29 months for bevacizumab) and median PFS was similar (10.4 *vs.* 10.8 months). After expanded RAS analysis, objective response rates were significantly higher with cetuximab (69 *vs.* 54 percent), median overall survival was similar (32 months for cetuximab and 31.2 months for bevacizumab) and median PFS was similar. There were no benefit the dual antibody therapy (EGFR targeted therapies and bevacizumab together) in the BOND-2, PACCE and CAIRO-2 trials [58-60].

Patients with refractory disease

Regorafenib: Regorafenib is a small molecule inhibitor of VEGF receptors 1 to 3 and oncogenic receptor tyrosine kinases. It has efficacy in a salvage therapy in metastatic colorectal cancer. Median overall survival was higher for patients receiving regorafenib compared with placebo (6.4 *vs.* 5.0 months) in the phase 3 CORRECT trial [61]. Regorafenib was also had an improvement of PFS (1.9 *vs.* 1.7 months). The most common severe toxicities observed with regorafenib were hand-foot skin reaction, fatigue, diarrhea, and hypertension. Regorafenib is FDA approved as a salvage therapy option in patients with advanced colorectal cancer who have previously been treated with a fluoropyrimidine, oxaliplatin, irinotecan, a VEGF inhibitor and, if KRAS wild-type, an EGFR monoclonal antibody.

Trifluridin-tipiracil (TAS-102): TAS-102 is an oral cytotoxic agent that consists the nucleoside analog trifluridine and tipiracil, a potent thymidine phosphorylase inhibitör. In the phase II trial, TAS 102 had significantly prolonged median overall survival (9 *vs.* 6.6 months) [62]. In the phase 3 RECOURSE trial, TAS 102 was associated with a significant prolongation in median overall survival (7.1 *vs.* 5.3 months) [63]. The most frequently toxicities were gastrointestinal and hematologic.

Immunotherapeutic options

PD-1/PD-L1 Immune checkpoint inhibitors: Immune checkpoint inhibitors targeting the programmed death-1 (PD-1) pathway by binding to PD-1 or its ligand(s) (PD-L1/L2) have shown proof of efficacy in various malignancies since 2014 [64]. The importance of the immune system in the biology of CRC is underscored by the finding that infiltration of the tumor by specific T cell immune infiltrates is highly correlated with better disease free and overall survival at all tumor stages. MSI-H/dMMR colon cancers are commonly characterized by dense lymphocytic infiltrates indicating a potential activation of the host's immune system [65]. In the pivotal pilot study was investigated the role of pembrolizumab in patients with advanced colorectal cancer with cohorts identified by their MSI status (MSI-H/dMMR *vs.* MSS/pMMR) [66]. Single-agent pembrolizumab showed an activity only among patients with MSI-H/dMMR cancers 9 (Table 1). There was a more than 60% response rate and a more than 90% disease control rate with some patients experiencing durable response for more than a year.

Conclusion

Colorectal cancer is the one of the field we had advance on management for the past ten years. Median survivals have prolonged from 12 months to nearly 40 months during this period. We assume that by the passing time we will have much more knowledge about the cancer cell and pathophysiology and this will reflect positive effects on patient management and outcome.

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