Review Article

Systemic Treatment of Colon Cancer

Konda B, Bakirhan K and Rajdev L*

Department of Medical Oncology, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, USA

***Corresponding author:** Rajdev L, Department of Medical Oncology, Albert Einstein College of Medicine/ Montefiore Medical Center, 1695 Eastchester Road, Bronx, NY 10461, USA

Abstract

Colorectal cancer is the third most common cancer worldwide, and is the third leading cause of cancer mortality with an estimated 50, 310 deaths occurring in 2014 in the United States. There has been a steady decline in the incidence of colorectal cancer over the past 30 years, which is largely due to early endoscopic screening. Surgical management remains the mainstay of treatment for early and locally-advanced non-metastatic colon cancers, and in patients with initially resectable liver or lung-only metastases. Systemic therapies have shown to significantly improve outcomes when given in the neo-adjuvant and/or adjuvant setting in these patients, and when used as principal therapy in patients with unresectable metastatic disease. The addition of adjuvant chemotherapy in patients with Stage III and high risk stage II disease significantly improves recurrence free survival. Patients with oligometastatic Stage IV colorectal cancer (CRC) who receive post-operative chemotherapy have a median OS that exceeds 5 years in some studies. The advent of targeted molecular therapies has further helped improve outcomes in patients with metastatic CRC cancer. Patients with unresectable metastatic disease who receive a combination of systemic chemotherapy and targeted agents have a median overall survival over 2 years today. It is important that patients be exposed to all active agents during their disease course to achieve this survival benefit. In this review article we summarize important clinical trials that have led to an evidence-based approach to the management of colon cancer.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, and accounts for over 1 million new cases of cancer each year. It is the fourth most frequent cause of cancer death worldwide [1]. In the US, CRC is the third most common cancer [2], with an estimated 96,830 new cases diagnosed in 2014 [3]. CRC is the third leading cause of cancer mortality in the US [2] with 50,310 deaths predicted to occur in 2014 [3].

Most cases (80%) of colon cancer cases are sporadic [4]. Although increasing age appears to be a strong risk factor, several modifiable risk factors are widely recognized in the development of sporadic colon cancer. These include obesity, tobacco use, alcohol consumption, and certain dietary patterns such as diet rich in red meat, and low in fiber [5]. Other risk factors include inflammatory bowel disease, history of colonic polyps, and prior history of colon cancer [4,6].

Approximately 20% of patients with CRC have a familial predisposition with 5-10% of these cases inherited in an autosomal dominant fashion [7]. The two most common hereditary forms of CRC are hereditary non polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP). HNPCC (Lynch syndrome), is an autosomal dominant disorder with a high penetrance rate, and represents about 3% of all CRC cases [8]. Lynch syndrome is also associated with multiple extracolonic neoplasms, commonly involving the endometrium, stomach, and ovary [8]. HNPCC is associated with germ-line mutations in DNA nucleotide mismatch-repair (MMR) genes, with over 90% of them occurring in MLH1, MSH2 and MSH6 genes [9]. FAP accounts for about 2% of all CRC cases [7]. Multiple colonic adenomas develop at an early age and become malignant by the fourth-fifth decade of life. A highly penetrant germ-line APC mutation produces a truncated protein which can be detected by PCR in most FAP patients [10].

Colon cancer can be divided into 4 stages based on the TNM staging system. This is presented in a simplified version in Table 1 [11]. Stages I and II are categorized as early-stage colon cancer, stage III as locally-advanced cancer, and stage IV as metastatic disease [12]. Surgery can be curative not only in patients with early-stage and locally- advanced colon cancer, but also in patients with liver-only or lung-only metastases (oligometastatic disease). For instance, hepatic metastetectomy results in a 38 percent 5-year survival in patients with liver-only metastases [13]. Systemic chemotherapy used before and/or after surgical resection has shown to significantly improve outcomes in patients with locally-advanced and oligometastatic CRC [14,15]. The use of systemic chemotherapy in combination with targeted molecular therapies in patients with unresectable metastatic CRC has improved median OS to over 2 years today [16-19]. Nonetheless, CRC has a 35% disease-specific mortality [20] and this demands heightened awareness of the treatment options in these patients.

Systemic chemotherapy in the adjuvant setting

Adjuvant therapy refers to treatment given in addition to, or following primary, oftentimes surgical treatment. It is aimed at elimination of residual microscopic disease, with the intention of cure and to lower the risk of cancer recurrence. Adjuvant chemotherapy plays no role in stage I colon cancer given a 93.1% five-year survival with surgery alone [21]. The important trials in patients with stage II and III CRC are detailed in Table 2.

5-Fluorouracil (5FU) is an antimetabolite and pyrimidine analogue, which acts by irreversible inhibition of the enzyme

Table 1: Simplified Colon cancer staging (11).

Stage (TNM)	Description
I	T1N0 and T2N0 (Tumor invades submocosa and muscularis propria)
II	IIA, IIB, IIC (T3N0 through T4bN0 -tumor invades through muscularis propria, through the viscera and directly invades or adherent to other organs, respectively, without nodal involvement)
III	IIIA, IIIB, IIIC (T1-T4B and N1-N2b without distant metastatic spread)
IV	IVa and IVb (any T, any N, M1a and M1b, respectively)

Table 2: Role of adjuvant chemotherapy in Stage I, II, and III CRC.

Stage	Group A [*]	Group B*	5-yr DFS[#] (%) (A v B)	p-value	5-yr OS[#] (%) (A v B)	p-value
II	Bolus 5FU/LV [26] (IMPACT)	S alone	71 v 62 (3-yr EFS)	NR	83 v 78 (3-yr OS)	NR
II and III	5-FU based [**] [38] (MSS and MSI-L tumors)	S alone (MSS and MSI-L tumors)	70 v 59	0.01[^]	76 v 68	0.02[^]
II and III	5-FU based [**] [38] (MSI-H tumors)	S alone (MSI-H tumors)	69 v 83	0.11[^]	71 v 88	0.07[^]
II and III	5FU based [39] pMMR patients	S alone	64 v 53	0.02[+]	71 v 62	0.11[+]
II and III	5FU based [39] dMMR patients	S alone	72 v 76	0.56[+]	75 v 81	0.95[+]
MOSAIC trial and subgroup analysis						
II and III	FOLFOX4 [15] (MOSAIC)	Infusion 5FU/LV	73 v 67	0.003	79 v 76 (6-yr OS)	0.046
II	FOLFOX4 [15] (MOSAIC subgp analysis)	Infusion 5FU/LV	84 v 80	0.258	87 v 87 (6-yr OS)	0.986
III	FOLFOX [15] (MOSAIC subgp analysis)	Infusion 5FU/LV	66 v 59	0.005	73 v 69 (6-yr OS)	0.023
NSABP C-07 trial and subgroup analysis						
II and III	FLOX [31,119] (NSABP C-07)	Bolus 5FU/LV	69 v 64	0.002	80 v 78	0.08
II	FLOX [119] (NSABP C-07 subset analysis)	Bolus 5FU/LV	82 v 80	0.67	90 v 90	0.84
III	FLOX [15] (NSABP-C07 subset analysis)	Bolus 5FU/LV	64 v 58	<0.001	77 v 74	0.052

[#]All percentages for DFS/EFS/OS have been rounded off to the nearest decimal; [*] All patients had surgical resection (S); [**] 5FU/Levamisole or 5FU/LV; [^] univariate analysis; [+] multivariate analysis

thymidylate synthetase involved in DNA replication, and forms the chemotherapy backbone in CRC [22]. 5-FU has predominantly gastrointestinal side effects, such as nausea, vomiting, diarrhea, and stomatitis. Other reported toxicities are palmar-plantar erythrodysesthesia (hand-foot syndrome), and leukopenia [23].

Leucovorin (LV) is a reduced form of folic acid that acts synergistically with 5-FU, trapping thymidylate synthetase in its inactive form [24], and thus enhancing 5-FU's antimetabolite effect [25]. Since the late 1980s, 5-FU and LV therapy have become the standard first-line adjuvant chemotherapeutic options in advanced CRC. The addition of LV to 5FU produces a two-fold increase in response rate compared to 5-FU monotherapy (21% v 11%; odds ratio (OR), 0.53; 95% CI, 0.44 to 0.63; p, <0.0001) [26].

The IMPACT investigators conducted a pooled analysis of three large randomized trials comparing adjuvant 5FU/LV to surgery alone in patients with colon cancer where the tumor has penetrated the bowel wall, without or without lymph node involvement [27]. Patients who received adjuvant 5FU/LV had a higher 3-year event free survival (EFS) (71% v 62%), a greater OS (83% v 78%), a 22% reduction in mortality (p, 0.029), and a 35 percent reduction in events (p, < 0.0001) when compared to those who had surgery alone [27].

Toxicities of 5FU are largely dependent on the mode of administration, with better tolerability when given as a continuous infusion via a portable pump when compared to bolus administration. In addition, infusion 5FU is associated with significantly higher response rates (30% for infusion 5FU v 7% for bolus 5FU; p, <0.001) [28]. However, an infusion pump requires central venous access which has potential thrombotic and infectious complications.

This led to the development of **capecitabine (xeloda)**, an oral pro-dug of 5FU. Capecitabine undergoes a multi-step reaction before its conversion to active 5-FU. The Xeloda colorectal cancer group conducted a large phase III multicenter randomized clinical trial (RCT) that compared infusion 5-FU to capecitabine. Capecitabine was non-inferior to 5FU, with fewer cases of stomatitis, alopecia, and neutropenia, but with a higher incidence of hand-foot syndrome and hyperbilirubinemia [29]. The X-ACT trial showed that adjuvant capecitabine had comparable disease-free survival (DFS), better relapse-free survival (HR 0.86; p, 0.04), similar OS, and significantly fewer adverse events when compared to the adjuvant 5-FU/LV group of patients with stage III colon cancer [30].

Oxaliplatin is another chemotherapeutic agent used in the adjuvant setting in colon cancer. It is a third generation antineoplastic platinum agent that inhibits DNA cross-linking. It has enhanced antitumor activity when used in combination with 5-FU/LV. Peripheral neuropathy is a common and dose-limiting toxicity of oxaliplatin [16,31,32]. Other common side effects include nausea, vomiting, diarrhea, liver sinusoidal injury, elevation in transaminases and alkaline phosphatase, thrombocytopenia, and hypersensitivity reactions [33].

In the pivotal MOSAIC trial, stage II and III colon cancer patients

were randomized following resection with curative intent, to receive either 5-FU/LV or 5-FU/LV plus oxaliplatin (FOLFOX4) [34]. Patients in the oxaliplatin-containing group had a 23% reduction in the risk of recurrence at 3-year median follow-up. A subgroup analysis of stage II patients showed no difference in OS between the two groups [16]. In another phase III trial (NSABP C-07), that included patients with stage II and III colon cancer, there was a significant improvement in DFS with the addition of oxaliplatin to 5-FU/LV (FLOX) regimen (4-year DFS: 73.2% for FLOX v 67% for 5-FU/LV) [32]. This led to FOLFOX being the new standard of treatment.

Adjuvant chemotherapy for stage II disease remains controversial, with survival rates of 82.5% with surgery alone [21]. Various prognostic factors and tools have been investigated to assist with risk stratification and identification of those stage II patients who would benefit from adjuvant chemotherapy.

High-risk clinicopathologic features include T4 tumors, poorly differentiated tumors, presence of lymphovascular invasion, perineural invasion, or bowel obstruction, pre-operative elevation in CEA levels, close, indeterminate, or positive margins, and inadequately sampled lymph nodes [16,35,36]. Additionally, genetic alterations have been used as predictive markers for response to chemotherapy. MMR genes, primarily MLH1 and MSH2 are responsible for the production of MMR proteins that are involved in the repair of microsatellite instability (MSI) occurring during DNA replication. Mutations in MMR genes are seen in HNPCC [7], and may occur in about 15% of patients with sporadic colon cancer [37]. This leads to MSI that can be categorized based on degree of instability into MSI- high (MSI-H), MSI- low (MSI-L), or microsatellite stable (MSS) [37].

MMR status is a prognostic and predictive factor in colon cancer. The presence of an MMR gene mutation correlates with a better prognosis. In fact, patients who express MMR gene proteins i.e. MMR proficient (pMMR) patients have been shown to have an increased rate of death from recurrent disease compared to their MMR deficient (dMMR) counterparts (32.8% v 8.8%; p, <0.0001). Similar outcomes were noted in MSI-L/MSS v MSI-H patients (35.1% v 10.7%, p, 0.0002) [38].

While survival is better for dMMR patients, these patients may have a detrimental outcome with adjuvant chemotherapy [39,40]. Ribik et al. showed that in the absence of adjuvant chemotherapy, patients with MSI-H tumors had significantly longer OS than patients with MSI-L and MSS tumors (HR for death, 0.31, 95% CI, 0.14-0.72; p, 0.004). When analysis was limited to the group receiving adjuvant chemotherapy, patients with MSI-L and MSS benefited from chemotherapy, while MSI-H patients did not (HR for death, 2.17; p, 0.10) [39]. Sargent et al. also demonstrated that when compared to surgery alone, adjuvant 5FU improved DFS in pMMR patients (HR, 0.67; p, 0.02), while this benefit was not seen in dMMR patients receiving adjuvant chemotherapy (HR, 1.10; p, 0.85). Moreover, adjuvant chemotherapy in stage II dMMR patients led to a lower OS in comparison to surgery alone (HR, 2.95; p, 0.04) [40]. Multiple gene assays have been developed for stage II and III colon cancer patients to identify those who would benefit from chemotherapy. Oncotype DX colon cancer assay measures the expression of seven recurrence risk genes and five reference genes, and has been shown to adequately estimate recurrence risk [41], with higher scores corresponding to an

increased absolute benefit with oxaliplatin therapy [42].

Adjuvant systemic chemotherapy in elderly patients

Elderly patients (65 years and older) have the highest incidence of colon cancer [20] and are often underrepresented in large clinical trials. The decision on chemotherapy in this group can be challenging given their multiple comorbidities and medical unfitness for chemotherapy. A pooled analysis of seven phase 3 RCTs evaluating the role of 5FU-based chemotherapy in patients with resected stage II or III colon cancer, showed a higher 5-year OS in patients who received adjuvant chemotherapy (71% v 64%; (HR, 0.76; 95% CI, 0.68 - 0.85). There was no significant interaction between age and efficacy of treatment. The incidence of toxicities was not increased among patients older than age 70, except for an increased risk of leukopenia in one study [43].

To further support these findings, a recent subgroup analysis of the MOSAIC trial established no statistically significant interaction between DFS, time to recurrence, or OS among 315 stage II and stage III patients aged between 70 and 75 who received chemotherapy with 5-FU/LV and oxaliplatin (FOLFOX) versus 5-FU/LV alone [44] .

Metastatic Colorectal Cancer (mCRC)

Patients with CRC with distant metastases at initial diagnosis (also known as synchronous metastases [45]) account for approximately 20% of all colorectal cancers, and have only a 12% five-year survival rate [20]. Patients with early-stage or locally advanced disease, who later develop metastatic disease (also known as metachronous metastases [45] account for 20-25% of all CRC cases [46].

Surgical treatment of mCRC

Patients with CRC with isolated liver or lung metastasis can potentially be cured surgically. With advances in surgical techniques and use of perioperative chemotherapy, the median survival in patients with liver-only or lung-only metastasis undergoing surgical resection, has risen close to 5 years, with minimal operative mortality. These patients can either be treated with surgery upfront or with chemotherapy prior to surgery. Tables 3 and 4 detail the survival statistics following metastatectomy in patients with liver-only and lung-only metastasis respectively. Patients with potentially resectable disease can be given chemotherapy in an attempt to make the tumor resectable (referred to as conversion therapy) [47]. Studies have shown that 12.5% to 36% of patients with initially unresectable/ potentially resectable liver-only metastasis, were successfully resected after conversion therapy with 5FU/LV, oxaliplatin, and/or irinotecan [48-51]. More recently, the addition of cetuximab to chemotherapy (arm A) in Chinese patients with initially unresectable KRAS WT colorectal liver-only metastases, was compared to chemotherapy alone (arm B). Patients in arm A had a significantly better rate of complete tumor resection (R0 resection: 25.7% v 7.4%; p, <0.01), a higher 3-year OS rate (41% v 18%; p, 0.013), and longer median survival time (30.9 v 21 months; p, 0.013) [52], when compared with patients randomized to arm B [52].

The role of postoperative chemotherapy with bolus 5FU/LV in patients with fully resected CRC metastases was evaluated in two randomized controlled trials- the ENG trial [53] and the FFCD 9002 trial [54]. The pooled analysis of these two trials demonstrated a trend to increased OS in patients who received adjuvant chemotherapy

Table 3: Survival following resection of Liver-only metastases in CRC.

Author	Year	No. of patients	% of pts who received CT^	Synchronous /Metachronous metastases	Operative mortality (%)	Median survival# (mo)	5-yr survival (%)	10-yr survival (%)	Median F/u (mo)
Scheele et al. [120]	1960-1992	434	0 systemic	44/56	4	40	39	24	NR
Tomlinson et al. [121]	1985-1994	612	NR	NR	5	44	35	17	NR
Choti et al. [122]	1984-1999	226	52*b	30/70	1	46	40	26	121 (1984-1992) 22 (1993-1999)
Fong et al. [123]	1985-1998	1001	NR	29/71	3	42	37	22	32
Wei et al. [124]	1992-2002	423	32c	32/68	2	53	47	28	31
Morris et al. [125]	1998-2004	3116	NR	NR	NR	NR	44	NR	?36
Giuliante et al. [126]	1992-2007	251	35b	41/59	1	46	39	24	37 (mean)

#All numbers and percentages for PFS/OS have been rounded off to the nearest decimal; *No. of patients who received post-op chemotherapy was not reported; b received pre-operative chemotherapy; c received chemotherapy post-hepatectomy; ^CT, chemotherapy

Table 4: Survival following resection of Lung-only metastases in CRC.

Author	Year	No. of patients	% of pts who received chemo	Operative mortality# (%)	Median survival# (mo)	5-yr survival (%)	10-yr survival (%)	F/u (mo) median
Kanzaki et al. [127]	1980-2008	156	49	0	43**	56	NR	NR
Iida et al. [128]	1990-2008	1030	23*	NR	70	54	38	40
Onaitis et al. [129]	1998-2007	378	68	1	NR	56	NR	NR
Blackmon et al. [130]	2000-2010	229	50	0	70	55	NR	37

#All numbers and percentages for survival/operative mortality have been rounded off to the nearest decimal; *575 patients had missing chemotherapy data; **Median time interval between first pulmonary resection and death or last follow-up exam

Table 5: Chemotherapy in the adjuvant or peri-operative setting in oligometastatic CRC.

Author	No. of patients	No. of patients in CT++ arm	No. of patients in Surgery alone (S) arm	PFS# (CT v S) (mo)	p-value	Median OS# (mo)	p-value
Mitry et al. [13]	278	138*	140	28 v 19	0.058	62 v 47	0.095
Nordlinger [14]	364	182**(all) 171(eligible) 152(resected)	182(all) 171(eligible) 152(resected)	20 v 13 21 v 13 NR	0.068 0.035 NR	61 v 54 64 v 55 78 v 73	0.34 0.30 0.35

#All numbers for PFS and OS have been rounded off to the nearest decimal; ++CT, chemotherapy; *Adjuvant chemotherapy; **Peri-operative chemotherapy

(Table 5) [14]. The use of perioperative chemotherapy (FOLFOX4) in patients with resectable liver-only metastasis was compared to surgery alone in the EORTC Intergroup Trial 40983. No difference in OS was noted between the two groups [15].

The timing of hepatectomy in patients with synchronous metastases remains unclear. In a systematic review and meta-analysis of 17 studies including patients with CRC with synchronous liver metastases, there were no differences in OS estimates and recurrence free survival (RFS) in patients who underwent simultaneous resection of both the colonic tumor and liver metastases, compared to those who underwent delayed hepatectomy. There was a greater incidence of postoperative complications in the latter group [46]. Unfortunately, most of the patients with metastatic CRC have unresectable disease [55,56]. Systemic chemotherapy and more recently, the addition of biological agents to chemotherapy has shown promise in the management of these patients.

Systemic therapy in mCRC

In a RCT conducted in 1993 by Scheithauer et al., patients who received systemic chemotherapy had a 6 month OS benefit when compared to those who received best supportive care (BSC) alone

[57]. Several chemotherapeutic agents have been shown activity in mCRC, including 5-FU/ LV, Oxaliplatin, and Irinotecan. Table 4 lists the important studies conducted in patients with metastatic unresectable CRC.

The use of 5-FU in metastatic colorectal cancer dates back several decades. Over the years, infusional 5-FU replaced bolus 5-FU, and combination 5-FU-based chemotherapy replaced single-agent 5-FU [58]. Studies have shown that LV when added to 5-FU increases response rates when compared to 5-FU alone [59,60]. The addition of oxaliplatin to 5-FU/LV (FOLFOX4) resulted in a longer PFS (median, 9.0 v 6.2 months; p, 0.0003) and a higher response rate (50.7% v 22.3%; p= 0.0001) compared to 5-FU/LV alone [61]. The median OS favored the FOLFOX4 arm but the difference did not reach statistical significance (16.2 v 14.7 months; p, 0.12).

The discovery of capecitabine led to studies comparing capecitabine plus oxaliplatin (CapeOX) and FOLFOX [62,63]. A meta-analysis of 7 randomized controlled trials (RCTs) showed no difference in PFS or OS in patients receiving CapeOX versus a combination regimen of 5FU/LV and oxaliplatin [64].

Irinotecan is a chemotherapeutic agent derived from the plant

Table 6: Treatment of mCRC in the first-line setting.

Author	Group A	Group B	PFS/TTP[#] (A v B) (mo)	p-value	Median OS[#] (A v B) (mo)	p-value
De Gramont et al. (Phase III) [60]	FOLFOX4[˙]	5FU/LV[¨]	9 v 6 (PFS)	0.0003	16 v 15	0.12
Colucci et al. [a] (Phase III) [73]	FOLFOX4	FOLFIRI	7 v 7 (TTP)	0.64	15 v 14	0.28
Hurwitz et al. (Phase III) [83]	FOLFOX4/ Bevacizumab	FOLFOX4	11 v 6 (PFS)	<0.001	20 v 16	<0.001
Saltz et al. (Phase III) [131]	FOLFOX4 (CapeOx)/ bevacizumab	FOLFOX4	9 v 8 (PFS)	0.0023	21 v 20	0.077
Bokemeyer et al. [94] (Phase II; OPUS)	FOLFOX4 / Cetuximab	FOLFOX4	8 v 7[++] (PFS)	0.0064[++]	23 v 19[++]	0.39[++]
Van Cutsem et al. [18] (Phase III)	FOLFIRI/ Cetuximab	FOLFIRI	10 v 8[++] (PFS)	0.0012[++]	24 v 20[++]	0.0093[++]
Douillard et al. [109] (Phase III; PRIME updated)	FOLFOX4/ Panitumumab	FOLFOX4	10 v 9 (PFS)	0.01	24 v 20	0.17/0.03[u]
Schwartzberg et al. [17] (Phase II; PEAK)	mFOLFOX6[˙˙˙]/ Panitumumab	mFOLFOX6[˙˙˙]/ Bevacizumab	Similar[++] Favored A[^] (PFS)	0.35[++] 0.029[^]	34 v 24[++] 41 v 29[^]	0.009[++] 0.058[^]
Heinemann et al. [16] (Phase III; FIRE-3)	FOLFIRI/ Cetuximab	FOLFIRI/ Bevacizumab	10 v 10[++] (PFS)	0.69[++]	29 v 25[++]	0.0164[++]
Stintzing et al. [102] (Phase III; FIRE-3)	FOLFIRI/ Cetuximab	FOLFIRI/ Bevacizumab	11 v 10[^] (PFS)	0.627[^]	33 v 26[^]	0.010[^]

[#]All numbers for PFS/OS/TTP have been rounded off to the nearest decimal; [¨]5FU/LV: 2-hour infusion of LV (200 mg/m^2/day) followed by a 5FU bolus (400 mg/m^2/day) and 22-hour infusion (600 mg/m^2/day) for 2 consecutive days every 2 weeks ; [˙]FOLFOX4: 5FU/LV with oxaliplatin 85 mg/m^2 as a 2-hour infusion on day 1; [˙˙˙]Modified FOLFOX6 regimen; [++]Data is for KRAS WT in exon 2 patient group only; [^]Data for WT KRAS and NRAS in exons 2,3,4; [a]Patients with locally advanced disease were also included; [u]updated analysis

alkaloid camptothecin [65]. It is hydrolyzed by the liver to its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38) [66]. Irinotecan and SN-38 exhibit antitumor activity by inhibiting the intracellular enzyme DNA topoisomerase I [67,69] .SN-38 undergoes glucuronidation and inactivation in the liver by the enzyme UGT1A1 [70]. This is clinically important, as patients with low UGT1A1 activity (example: Gilbert's syndrome) are predisposed to increased drug-related toxicity [70]. The common side effects of irinotecan include nausea, vomiting, diarrhea, cholinergic symptoms, and alopecia [71,72].

The use of irinotecan in combination with BSC in patients who failed prior 5-FU based therapy, was compared to BSC alone in a randomized trial by Cunningham et al. Patients who received single-agent irinotecan had a higher 1-year survival compared to the BSC alone group (36.2 v 13.8%; p, 0.0001). In the LIFE study, a median OS of 15.9 months was noted in patients receiving single agent irinotecan as second-line therapy following failure of oxaliplatin plus 5-FU/LV [73].

A combination chemotherapy regimen of irinotecan added to 5FU/LV (FOLFIRI) was compared to 5FU/LV alone in a phase III randomized trial by Douillard et al. Patients randomized to the FOLFIRI arm had a higher response rate (49% v 31%; p, <0.001), longer time to progression (TTP) (6.7 v 4.4 months; p, <0.001), and longer median OS (17.4 v 14.1 months; p, 0.031) compared to the no-irinotecan arm [72]. FOLFIRI was compared to FOLFOX4 in previously untreated patients with locally advanced and/or metastatic CRC. There was no difference overall response rate, PFS, and OS between the two treatment groups [74].

Both FOLFOX6 and FOLFIRI have been shown to be active in patients refractory to prior fluoropyramidine therapy [75,76]. The sequencing of these regimens is often determined by their toxicity profiles, as outcomes are similar regardless of which one is given first. A phase III trial comparing untreated mCRC patients who had

received FOLFIRI followed by FOLFOX6 (arm A) on progression or FOLFOX6 followed by FOLFIRI (arm B) on progression produced similar results in both arms (first-line PFS 8.5 months in arm A v 8.0 months in arm B), and OS (21.5 months in arm A v 20.6 months in arm B) [77].

Treatment interruptions are not uncommon. Often, adverse effects of chemotherapy or worsening of patient's performance causes providers to hold chemotherapy until improvement of the above. A meta-analysis presented at 2014 ASCO Annual Meeting [78] included 6 RCTs that assessed the effect of chemotherapy delivered continuously until progression versus in 3.7-4.3 month interruptions. Chemotherapy delivered until progression was associated with modest but significant improvement in OS (HR, 0.89; p, 0.01; I^2 0%). This was, not surprisingly, associated with more adverse effects and impaired quality of life [78].

Targeted therapies

The advent of targeted agents led to trials evaluating the role of combining various chemotherapeutic agents with targeted agents.

Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor-A (VEGF-A) [79,80] VEGF blockade results in decreased tumor vessel permeability and tumor vessel size [81], inhibition of tumor neovascularization [82], and induction of endothelial and tumor cell apoptosis [83]. Bevacizumab is FDA approved for the treatment of mCRC in combination with chemotherapy [84]. Common adverse effects include hypertension, proteinuria, hemorrhage, delayed wound healing, and venous thromboembolism [84,85].

In a phase III trial by Hurwitz et al., over 800 untreated mCRC patients were randomly assigned to receive *irinotecan/bolus 5FU/LV (IFL)* with or without bevacizumab. The addition of bevacizumab to chemotherapy was associated with a striking improvement in PFS and OS when compared to chemotherapy alone (Table 6) [84], leading to FDA approval of bevacizumab in the first-line setting. The

E3200 trial showed that the addition of bevacizumab to FOLFOX4 in previously treated mCRC patients was also associated with a benefit in OS (12.9 v 10.8 months; p, 0.0011) and PFS (7.3 v 4.7 months; p, <0.0001) when compared to the FOLFOX4-only group [86]. This led to bevacizumab's approval in combination with a 5FU-based regimen, in the second-line setting as well.

Bevacizumab in combination with chemotherapy has also been shown to be safe in medically fit elderly patients who derive benefits similar to their younger counterparts. The combination of capecitabine and bevacizumab was tested in treatment naive elderly patients (median age 76 years) with unresectable mCRC, in a phase III open-label study (AVEX trial). PFS favored the capecitabine plus bevacizumab arm (9.1 v 5.1 months; HR, 0.53; p, <0.0001), with a trend towards an OS advantage (20.7 v 16.8 months; HR, 0.79; p, 0.18) when compared to the capecitabine-only arm. The frequency of treatment related grade 3 or higher adverse effects were similar in both groups except for a higher rate of hand-foot syndrome and venous thromboembolic events in the bevacizumab containing arm. Thus, in the appropriate setting, the addition of bevacizumab is safe and effective in medically fit elderly patients [87].

Continuation of bevacizumab beyond progression has been shown to confer a survival advantage. In a phase III trial, continuation of bevacizumab in combination with second-line chemotherapy in patients who had POD on first-line therapy plus bevacizumab, resulted in a longer median OS when compared to the no-bevacizumab arm (11.2 v 9.8 months; HR, 0.81; unstratified log-rank test, 0.0062) [88].

Cetuximab (C225) is a human-mouse chimeric IgG1 monoclonal antibody against epidermal growth factor receptor (EGFR) [89]. EGFR is over expressed in various human cancers [90]. Cetuximab exerts its anti-tumor effect by competitively inhibiting binding of ligand to EGFR. It thus inhibits activation of receptor tyrosine kinase, thereby interfering with cellular function [91-93]. Diarrhea, skin rash, infusion reactions, and hypomagnesemia are some of its side effects [19,94-96]. This drug is FDA approved for use in patients with KRAS wild-type (WT) mCRC [19].

KRAS is a protein involved in the EGFR signaling pathway and mutations in the encoding KRAS gene, especially at exon 2 predict a poor response to anti-EGFR therapy [96-99]. The encouraging results of a phase III randomized controlled trial by Cunningham et al., comparing the efficacy of cetuximab plus irinotecan versus cetuximab alone in irinotecan-refractory patients with mCRC, led to FDA approval of cetuximab both as monotherapy and in combination with irinotecan in this setting [100]. Subsequently, FDA approval of cetuximab was extended to the frontline setting as well. Two large randomized studies (CRYSTAL and OPUS) played a key role in the drug's approval. In both trials patients' tumors were retrospectively analyzed for KRAS mutation status. The OPUS (phase II, FOLFOX4 with or without cetuximab) [96] and CRYSTAL (phase III, FOLFIRI with or without cetuximab) [99] trials supported the benefit of addition of cetuximab to common chemotherapy regimens with improvement in PFS in KRAS WT patients (Table 6). It is of note that patients with mutant-KRAS status who received cetuximab plus chemotherapy had a worse outcome compared to those who received chemotherapy alone [96,99]. BRAF protein is another biomarker that is encoded by the BRAF gene. A mutation in the BRAF oncogene leads to activation of the MAP kinase pathway and appears to be mutually exclusive of KRAS mutation status [101,102]. The presence of a BRAF mutation is not predictive of anti-EGFR treatment response or resistance, but has been shown to be a negative prognostic marker in patients with KRAS WT tumors [102,103].

In the first head-to-head comparison of cetuximab versus bevacizumab (FIRE-3), patients were randomized to receive FOLFIRI with either cetuximab (Arm A) or bevacizumab (Arm B) in the first-line treatment of mCRC. Patients with WT KRAS mCRC who received cetuximab plus FOLFIRI, had a 3.7 month OS benefit when compared to patients who received bevacizumab plus FOLFIRI (Table 6) [17]. Interestingly, extended RAS testing (KRAS exons 2,3,4; NRAS exons 2, 3, 4) done as part of a pre-planned analysis, not only showed a 7.2 month survival benefit in patients with WT RAS tumors who received cetuximab, but also a 6.1 month PFS disadvantage in patients with mutated KRAS on exons 3/4 or mutated NRAS on exons 2/3/4, but a WT KRAS on exon 2, when compared to the bevacizumab-containing arm in each of the two groups of patients respectively [104]. Thus, extended RAS analysis appears to be a better predictive marker for treatment response to cetuximab therapy.

More recently, in the phase III CALGB/SWOG 80405 trial [105] presented at the 2014 ASCO Annual Meeting Plenary Session, the addition of cetuximab (Arm A) or bevacizumab (Arm B) to chemotherapy (73.4% FOLFOX and 26.6% FOLFIRI) in patients with untreated KRAS-WT metastatic CRC, produced comparable benefit in OS and PFS in both groups (OS: 29.93 v 29.04 months; PFS: 10.45 v 10.84 months, in arm A v arm B, respectively) [105].

Panitumumab (E7.6.3, ABX-EGF) is a fully humanized IgG2 monoclonal antibody against EGFR [106,107]. It inhibits the binding of epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-alpha) to EGFR, and thus inhibits cell proliferation [107]. Adverse effects include skin rash, hypomagnesemia, dryness of skin, and pruritus [108].

Panitumumab gained FDA approval based on the results of a phase III open-label trial comparing panitumumab with BSC versus BSC alone in patients with mCRC who progressed on standard chemotherapy, Patients who received panitumumab had higher PFS (8 weeks v 7.3 weeks; HR, 0.54; p, <0.0001) and a better response rate (10% v 0%; p, <0.0001) after at least 1 yr of follow-up, when compared to the BSC alone arm [109]. The phase III PRIME trial played a vital role in the drug's approval in the front-line setting in mCRC [110]. In this trial patients with KRAS WT tumors in exon 2 receiving panitumumab plus FOLFOX4 as frontline therapy, were noted to have a significant improvement in median PFS (10.0 v 8.6 months; HR, 0.8; p, 0.01) and median OS (23.9 v 19.7 months; updated HR, 0.83; updated p, 0.03), when compared to those receiving FOLFOX4 alone (Table 6). In KRAS mutated patients PFS and OS were lower in patients who received panitumumab plus FOLFOX4 versus FOLFOX4 alone [110]. As seen with cetuximab in the FIRE-3 trial, extended RAS mutation status was a better predictive marker of response or resistance to panitumumab containing therapy in the PRIME trial [111].

Other targeted agents

Ziv-Aflibercept (VEGF trap) is a recombinant protein produced

by fusion of the second immunoglobulin (Ig) domain of VEGFR1 and the third Ig domain of VEGFR2 with the constant region of human IgG1 [112]. The drug binds to VEGF-A, VEGF-B, and placental growth factor (PlGF) and blocks VEGF-mediated signaling [80]. This results in near-complete blockade of angiogenesis in tumor cells, and inhibition of tumor cell growth [112]. It is important to note that Ziv-Aflibercept has a much higher affinity to VEGF-A when compared to bevacizumab [80]. Adverse effects include fatigue, headache, hemorrhage, nausea, diarrhea, hypertension, and proteinuria [113-115] .

The combination of FOLFIRI with ziv-aflibercept in patients who failed prior oxaliplatin-based therapy (with or without bevacizumab), was studied in the phase III VELOUR trial. Patients were randomized to receive FOLFIRI plus ziv-aflibercept versus FOLFIRI alone. Both PFS and OS favored the Ziv-aflibercept containing arm (PFS: 6.90 v 4.67 months, HR, 0.758, p, <0.0001; OS: 13.50 v 12.06 months, HR, 0.817, p, 0.0032) [114].

Regorafenib is an orally administered multikinase inhibitor that exhibits anti-tumor activity by inhibiting kinases involved in oncogenesis and angiogenesis, and the kinases present in the stroma. These include RET, KIT, c-RAF/RAF1, B-RAF, B-RAFV^{600E} , VEGFR1, VEGFR2, VEGFR3, tyrosine kinase with immunoglobulin-like and EGF-like domains (TIE2), fibroblast growth factor receptor 1 (FGFR1), and platelet derived growth factor receptor beta (PDGFR-beta) [116]. Most frequent side-effects include diarrhea, loss of appetite, weight loss, hand-foot syndrome, skin rash, dysphonia, hypertension, oral mucositis, and low platelet count [117].

The CORRECT trial was a multicenter phase III trial that randomized patients with mCRC refractory to all standard treatment regimens (including fluoropyrimidine-, oxaliplatin-, irinotecan-, bevacizumab- based therapy; patients with KRAS WT tumors should have failed cetuximab or panitumumab-based treatment), to receive Regorafenib plus BSC versus placebo plus BSC . Patients in the regorafenib arm had a longer median OS compared to the placebo arm (6·4 v 5·0 months; HR, 0.77, one-sided p, 0·0052). Patients in the regorafenib group had a greater incidence of hand-foot syndrome, fatigue, hypertension, diarrhea, and skin rash [117].

In a retrospective analysis including patients who were exposed to all 5 agents (5FU, Oxaliplatin, irinotecan, cetuximab, and bevacizumab) during their course of treatment, patients who received a minimum of 8 weeks of, and 6 cycles of cetuximab in addition of 5FU, Oxaliplatin, and irinotecan, had a mean OS of 44.8 ± 11.03 months [118]. It is therefore important that receive all active agents to achieve adequate survival benefit.

Role of maintenance therapy

The phase III CAIRO3 trial randomized patients who received 6 cycles of CapeOx plus bevacizumab (CapeOx-B) to either maintenance capecitabine plus bevacizumab (Cape-B) or observation. Patients in either arm, who had progression of disease (PFS1), received CapeOx-B until second progression (PFS2; primary end point). Patients with synchronous metastases at baseline whose primary tumor was resected and who received maintenance Cape-B were noted to have a significantly longer median OS compared to those who had no maintenance therapy (25 v 18 months; log-rank p,

<0.0001; 2-yr median follow-up) [119]. Median PFS2 also favored the maintenance therapy arm (11.7 v 8.5 months; HR, 0.67; p, <0.0001) [120].

The need for maintenance therapy was further strengthened in the OPTIMOX2 trial where patients were randomized to receive 6 cycles of modified FOLFOX7 (Day 1: LV 400 mg/m², Oxaliplatin 100 mg/m²; Day 2: 5FU infusion 3000 mg/m²), followed by maintenance 5FU/LV versus 6 cycles of modified FOLFOX7 with no maintenance therapy. Patients who received maintenance chemotherapy had a longer duration of disease control (13.1 v 9.2 months; HR, 0.71; p, 0.046) and longer PFS (8.6 v 6.6 months; HR, 0.61; p, 0.0017) compared to the no-maintenance therapy arm [121].However, there was no significant median OS advantage with maintenance therapy (23.8 v 19.5 months; HR, 0.88; p, 0.42)

Conclusions

The use of systemic chemotherapy and targeted agents has markedly improved outcomes in patients with colon cancer. Understanding the pharmacology of each chemotherapeutic agent has helped clinicians and researchers combine therapies leading to a synergistic effect. Research in recent years has helped develop treatments tailored to patient and tumor characteristics. The relative resistance of certain tumors to conventional therapies is now better understood with the use of biomarkers in predicting response. While stage I and favorable risk stage II CRC can be cured with surgery alone, patients with high-risk stage II and stage III disease benefit from adjuvant chemotherapy. Surgery and perioperative chemotherapy can be potentially curative in patients with stage IV mCRC with oligometastatic disease. Patients with unresectable metastases are best treated with palliative intent chemotherapy with or without the use of targeted therapy, leading to a median overall survival of over 2 years. It is important that patients be exposed to all active agents to achieve this survival benefit.

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