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MINIREVIEWS

Novel therapeutic agents in the treatment of metastatic colorectal cancer

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Abstract

Over the past couple of decades considerable progress has been made in the management of metastatic colorectal cancers (mCRC) leading to a significant improvement in five-year survival. Although part of this success has been rightly attributed to aggressive surgical management and advances in other adjunct treatments, our understanding of the pathogenesis of cancer and emergence of newer molecular targets for colon cancer has created a powerful impact. In this review article we will discuss various targeted therapies in the management of mCRC. Newer agents on the horizon soon to be incorporated in clinical practice will be briefly reviewed as well.

Key words: Metastatic colorectal cancer; Molecular targeted drugs; Anti-angiogenesis inhibitors; Epidermal growth factor receptor inhibitors; Novel therapeutic agents

Core tip: This article reviews the novel agents in the management of metastatic colorectal cancer. The core principles and the evidence behind the use of these agents are discussed. Clinically relevant features are highlighted to help the health care provider involved in the care of metastatic colorectal cancer patients.

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INTRODUCTION

In 2015, a total of 132700 new cases of colorectal cancer are expected to be diagnosed in the United States accounting for about 8% of all new cancer diagnoses. In this same year 49700 patients will die of metastatic colorectal cancers (mCRC), which will contribute to 8.4%

of all cancer related mortality[1]. With the widespread use of screening colonoscopy and newer modalities like Stool DNA based screening, we can expect early diagnosis and curative treatments in patients diagnosed with early disease and hence better survival. However up to > 25% of patients will present with metastatic disease, where systemic treatment options will be desired. Widespread use of genetic screening and sharing platforms like the cancer Genome Atlas has led to a better understanding of carcinogenesis and as a consequence newer molecular targets for colon cancer have been discovered[2]. In this review article we will discuss some of the well-known targetable pathways as well as shed light on some of the novel pathways where we can expect newer therapies to emerge.

ANTI-ANGIOGENESIS AGENTS

Anti-angiogenesis was proposed as an anticancer therapy over four decades ago[3]. We know that angiogenesis is required for invasive tumor growth and metastasis and is an integral part of cancer progression[4]. Angiogenesis is mediated through vascular endothelial growth factor (VEGF), the altered regulation of which is associated with several diseases including malignancy. VEGF is a heparin-binding growth factor specific for vascular endothelial cells that is able to induce angiogenesis *in vivo*[5]. Three notable anti-VEGF agents have been approved by United States Food and Drug Administration (USFDA) for treating mCRC and will be reviewed here.

Bevacizumab

Bevacizumab is a recombinant humanized IgG-1 antibody against soluble VEGF-A which has a high binding specificity with VEGF-A. Once bound, Bevacizumab prevents its interaction with receptors on vascular endothelial cells and thereby truncates the abnormal downstream signaling. After success in early phase trials, this agent was tested in phase 3 clinical trials[6]. In the pivotal trial which had 813 previously untreated patients with mCRC randomized to the two arms, the median duration of survival was 20.3 mo in the Irinotecan, 5-Fluorouracil and Leucovorin (IFL) plus Bevacizumab group, as compared with 15.6 mo in the IFL plus placebo group, corresponding to a hazard ratio for death of 0.66 ($P < 0.001$)[7]. An Eastern Cooperative Oncology Group Study (E3200) showed median duration of survival for the group treated with FOLFOX4 and Bevacizumab was 12.9 mo compared with 10.8 mo for the group treated with FOLFOX4 alone (corresponding hazard ratio for death 0.75, $P < 0.001$), and 10.2 mo for those treated with Bevacizumab alone. Bevacizumab is approved by the USFDA in combination with either an Irinotecan or Oxaliplatin based regimen for the treatment of mCRC[8,9].

Bevacizumab is generally well tolerated when administered in combination with chemotherapy for mCRC. Hypertension, proteinuria, epistaxis and thrombosis are some of the common adverse events associated with its use[6]. No clear guidelines exist on the management of hypertension but in most patients it is usually possible to control hypertension with standard antihypertensive medications. On occasion, it may be necessary to temporarily or permanently discontinue Bevacizumab if hypertension is severe or persistent[10].

Routine use of Bevacizumab as maintenance therapy is controversial. A recent study found no clear benefits of continuing Bevacizumab after 4-6 mo of standard first-line chemotherapy plus Bevacizumab and given the cost and lack of clear benefit, it was not recommended[11]. Whether a certain subgroup with high-risk disease such as high metastatic burden would benefit from this approach needs further investigation[12].

Ziv-Aflibercept

Ziv-Aflibercept is a fusion protein consisting of human VEGF receptor extracellular domains fused to the Fc portion of human immunoglobulin G1, and works by inhibiting VEGF receptor. Aflibercept was used in a large phase 3 trial in combination with 5-Fluorouracil, Irinotecan and Leucovorin (FOLFIRI) and was found to confer a statistically significant survival benefit over FOLFIRI combined with placebo in patients with mCRC previously treated with an Oxaliplatin based regimen[13]. Adding Aflibercept to FOLFIRI showed an improved overall survival relative to placebo plus FOLFIRI (HR = 0.817, 95%CI: 0.713-0.937, $P = 0.0032$) with median survival times of 13.50 mo *vs* 12.06 mo, respectively. Efficacy was maintained across demographic and baseline characteristics and stratification factors at randomization, irrespective of prior treatment with Bevacizumab, with a similar safety profile[14].

Ramucirumab

Ramucirumab is a recombinant human monoclonal anti vascular endothelial growth factor-receptor 2 antibody which was recently approved by USFDA for use in combination with FOLFIRI for the treatment of patients with mCRC whose disease has progressed on first line Bevacizumab, Oxaliplatin- and Fluoropyrimidine-containing regimen. Approval was based on a study that enrolled 1072 patients (536 in each group) and patients were randomized either to receive Ramucirumab or placebo[15]. PFS was significantly improved in patients who received Ramucirumab in combination with FOLFIRI compared to placebo [Median PFS was 5.7 and 4.5 mo; HR = 0.79 (95%CI: 0.70-0.90, $P < 0.001$]. Median overall survival was 13.3 mo (95%CI: 12.4-14.5) for patients in the Ramucirumab group *vs* 11.7 mo (10.8-12.7) for the placebo group (HR = 0.844, 95%CI: 0.730-0.976, log-rank $P = 0.0219$). Diarrhea, hypertension and fatigue were the common adverse events with the use of Ramucirumab, consistent with the previously known safety profile established in previously approved indications.

EPIDERMAL GROWTH FACTOR RECEPTOR AND OTHER KINASES

The epidermal growth factor receptor (EGFR) autocrine pathway has been known to affect a number of processes important to carcinogenesis including cell proliferation, apoptosis and angiogenesis. This has been the rationale for developing EGFR inhibitors, both monoclonal antibodies to prevent ligand binding as well as small molecule inhibitors of the tyrosine kinase enzymatic activity to inhibit auto-phosphorylation and downstream intracellular signaling[16]. Although monoclonal antibodies like cetuximab were initially developed to treat head and neck cancer, traditionally known to highly express EGFR on immunohistochemistry, their use was extended to treating colorectal cancer.

Cetuximab: Cetuximab is a chimeric (mouse/human) monoclonal antibody used in the management of mCRC, which was initially approved by USFDA as a third line single agent in patients who have failed Oxaliplatin- or Irinotecan- based chemotherapy and who are intolerant to Irinotecan. In the pivotal trial which compared FOLFIRI plus Cetuximab *vs* FOLFIRI plus Bevacizumab as first-line treatment for patients with mCRC, 592 patients with KRAS exon 2 wild-type tumors were randomly assigned and received treatment. Median progression-free survival was 10.0 mo (95%CI: 8.8-10.8) in the Cetuximab group and 10.3 mo (95%CI: 9.8-11.3) in the Bevacizumab group (HR = 1.06, 95%CI: 0.88-1.26, *P* = 0.55); however, median overall survival was 28.7 mo (95%CI: 24.0-36.6) in the Cetuximab group compared with 25.0 mo (22.7-27.6) in the Bevacizumab group (HR = 0.77, 95%CI: 0.62-0.96, *P* = 0.017). Anti-EGFR monoclonal antibodies are well tolerated, the most important adverse event being cutaneous reaction including rash, pruritus, and nail changes. These adverse reactions can usually be medically managed and patients tend to continue on the drugs. Occasionally the drug may need to be discontinued due to intolerable side effects.

Panitumumab

Panitumumab is a fully humanized monoclonal antibody specific to EGFR. The efficacy of Panitumumab was established in the PRIME study which showed that in the wild-type KRAS stratum, Panitumumab-FOLFOX4 significantly improved PFS compared with FOLFOX4 (median PFS, 9.6 mo *vs* 8.0 mo, respectively; HR = 0.80; 95%CI: 0.66-0.97, *P* = 0.02). Also noted was a nonsignificant increase in OS for Panitumumab-FOLFOX4 *vs* FOLFOX4 (median OS, 23.9 mo *vs* 19.7 mo, respectively; HR = 0.83, 95%CI: 0.67-1.02, *P* = 0.072)[17]. In an open-label, phase 3 head-to-head study of Panitumumab *vs* Cetuximab which enrolled patients with chemotherapy-refractory mCRC Panitumumab was non-inferior to Cetuximab. Median overall survival was 10.4 mo (95%CI: 9.4-11.6) with Panitumumab and 10.0 mo (9.3-11.0) with Cetuximab (HR = 0.97, 95%CI: 0.84-1.11)[18]. Panitumumab has been shown to induce pathological near complete response or complete response when given along with neoadjuvant concurrent radiation therapy in patients with KRAS wild-type locally advanced rectal cancer[19]. Panitumumab is generally well tolerated and has a similar side effect profile as Cetuximab.

Ras testing and use of egfr antibodies

EGFR expression as measured by immunohistochemistry on many occasions does not predict clinical benefit with the use of EGFR inhibitors[20,21]. It has also been shown that mutations in the KRAS exon 2 (codons 12 and 13), which was down stream to EGFR, dictated the response to EGFR antibodies. Additional mutations like KRAS exon 3 (at codons 59 and 61) and exon 4 (at codons 117 and 146), NRAS exon 2 (at codons 12 and 13), exon 3 (at codons 59 and 61), and exon 4 (at codons 117 and 146), have been demonstrated to be negative predictive biomarkers for EGFR antibody treatment. These additional mutations now account for approximately 17% of patients with wild-type KRAS exon 2 status who harbor a mutation in other RAS exons[22]. Testing for extended EGFR mutation is highly recommended and if truly wild type then use of EGFR antibodies is justified in those cases.

TYROSINE KINASE INHIBITORS

Regorafenib (BAY 73-4506) is a novel oral diphenylurea based multikinase inhibitor, shown to be a potent inhibitor of a wide variety of Tyrosine kinases which include several angiogenic, stromal receptor and oncogenic tyrosine kinases as well as intracellular signaling kinases in preclinical studies[23]. A phase Ⅲ trial in refractory mCRC, (CORRECT) randomized 760 patients between Regorafenib (*n* = 505) and placebo (*n* = 255). It showed a small but statistically significant improvement in OS (median 6.4 mo *vs* 5 mo, one-sided *P* value 0.005) and progression-free survival (median 1.9 mo *vs* 1.7 mo, one-sided *P* value < 0.000001) for Regorafenib[24]. The most common side effects of Regorafenib are fatigue, hand-foot skin reaction (palmar-plantar erythrodysesthesia), diarrhea, mucositis and weight loss for which the patients need to be monitored closely[25]. A novel germline mutation of PDGFR-beta might be associated with clinical response of colorectal cancer to Regorafenib[26].

EMERGING AGENTS

Targeting cancer stem cells

Human cancers have been shown to harbor cancer stem cells which are thought to play an important role in cancer recurrence and metastasis. With the recent discoveries of small molecules that target highly conserved cell homeostasis pathways which have been implicated in the pathogenesis of colorectal cancer, gives us an

Table 1 Ongoing clinical trials in Immunotherapy in colorectal cancer

Drug name	Class	Phase	ClinicalTrials.gov Identifier	Sponsor	Remarks
AMP-224	PD-1 inhibitor	1	NCT02298946	NCI	Combination with stereotactic body radiation therapy
MPDL3280A	Engineered anti-PDL1 antibody	1	NCT01375842	Genentech	Administered as single agent
Varlilumab and nivolumab	Monoclonal antibodies that binds to CD27 and PD-1	1/2	NCT02335918	Celldex therapeutics/ bristol-myers squibb	Phase Ⅱ to determine objective response rate
MPDL3280A and bevacizumab	Engineered anti-PDL1 antibody	1b	NCT01633970	Genentech	Assess the safety, pharmacology and preliminary efficacy of the combination
Avelumab	Antibody targeting PDL-1	1	NCT01772004	EMD serono	Open-label, dose-escalation trial
MEDI4736	Anti PDL-1	2	NCT02227667	Memorial sloan Kettering cancer center	Study to evaluate the efficacy of MEDI4736

Available from: URL: http://www.clinicaltrials.gov, accessed on 4/25/2015.

exciting avenue in treating mCRC. BBI608, an orally-administered first-in-class cancer stem cell inhibitor, has been tried in a Phase 1 study after excellent preclinical evidence. This has shown some promising anticancer activity in patients with CRC[27]. An open label, multi-center, Phase 2 study of BBI608 in combination with cetuximab, Panitumumab or Capecitabine in patients with advanced colorectal cancer is ongoing (ClinicalTrials.gov Identifier: NCT01776307). Another phase 1 dose escalation study with LGK974 is currently ongoing and recruiting patients with special emphasis on those with B-RAF mutant colorectal cancer with documented Wnt pathway alteration (ClinicalTrials.gov Identifier: NCT01351103).

BRAF

BRAF mutations have been shown to be the cause of sporadic CRCs through altered mismatch repair pathway and occur mutually exclusive of *KRAS* mutations[28]. At this time *BRAF* mutation is known to confer a poor prognosis in mCRC, but is not a validated target for anti-cancer therapy[29,30]. Although this mutation is found in a relatively small proportion of CRC (5%-8%), targeting BRAF has been unsuccessful as feedback stimulation of EGFR pathway has been suggested as the reason for the treatment failure[31]. Current studies are focused on dual blockade of BRAF and EGFR or of the subsequent downstream pathway. Initial experience of combining BRAF inhibitor Vemurafenib with EGFR inhibitor Panitumumab has been safe, although the response has been modest[32]. Another Phase Ⅱ Study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF mCRC is still recruiting patients (ClinicalTrials.gov Identifier: NCT02164916). Another potential strategy is the use of ERK inhibitor that is thought to suppress MAPK activity, which is usually upregulated in patients on RAF inhibitors and may overcome resistance. ERK inhibitors are currently in early phase clinical trials[33].

Immunotherapy

The advent of immune check point blockade has been an exciting field in cancer immunotherapy. Already of considerable success in other types of cancers like melanoma and squamous cell lung cancer where Anti PD-1 drugs are approved by USFDA, various groups are studying the efficacy in colorectal cancer. Mismatch-repair status has been useful in predicting clinical benefit of immune checkpoint blockade with Pembrolizumab, with higher response in Microsatellite Instability High (MSI-High) tumors[34]. The table summarizes the current ongoing trials mainly targeting PD-1 - PDL-1 immune checkpoint pathway (Table 1).

Targeting kras with reolysin

Biological strategies like Reovirus Serotype 3 - Dearing Strain (Reolysin), a naturally occurring ubiquitous, non-enveloped human Reovirus, have been explored in mCRC for targeting KRAS. Reovirus has been shown to replicate selectively in RAS-transformed cells causing cell lysis. Activating mutations in RAS or mutations in oncogenes signaling through the RAS pathway may occur in as many as 80% of human tumors and can be targeted by this approach. A multicenter phase 1 study Reolysin in combination with FOLFIRI and Bevacizumab in FOLFIRI naive patients with KRAS mCRC is ongoing (ClinicalTrials.gov Identifier: NCT01274624).

TAS-102

TAS-102 is a novel oral nucleoside and works as an antimetabolite. TAS-102 is a combination of trifluridine, a nucleoside analog, and tipiracil hydrochloride, a thymidine phosphorylase inhibitor. In a double-blind, randomized, placebo-controlled phase 2 trial, 112 patients were allocated to TAS-102 and 57 allocated to placebo. Median overall survival was 9.0 mo (95%CI: 7.3-11.3) in the TAS-102 group and 6.6 mo (4.9-8.0) in the placebo group (hazard ratio for death 0.56, 80%CI: 0.44-0.71, 95%CI: 0.39-0.81, P = 0.0011) on a median follow up of 11.3 mo (interquartile range 10.7-14.0 mo). Hematological toxicities were the important side effects to consider in patients on TAS- 108 arm, 57 (50%) neutropenia of grade 3 or 4, 32 (28%) leucopenia and 19 (17%) experiencing anemia. Serious adverse events were reported in 21 (19%) patients in the TAS-102 group. Recent data from RECOURSE study has shown that median overall survival improved from 5.3 mo with placebo to 7.1 mo with TAS-102. Hazard ratio for death

in the TAS-102 group *vs* the placebo group was 0.68 (95%CI: 0.58-0.81, $P < 0.001$), and this data led to its FDA approval[35].

CONCLUSION

In conclusion, mCRC treatment is a rapidly evolving field with many novel agents under investigation. Although many targeted drugs have been approved and are already in clinical use, there is a clear need for further research and development of more effective treatments. Over the coming years, as understanding of the biology of the disease improves, newer treatment modalities will be investigated. The optimum use and sequencing of these agents, especially in combination with chemotherapy and other targeted agents will need to be better defined.

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