How I Treat Chemorefractory Metastatic Colorectal Cancer

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Learning Objectives

- Identify the most appropriate systemic therapies for patients with chemorefractory metastatic colorectal cancer

- Determine the role of molecular sequencing in identifying genome-driven therapies for patients with chemorefractory metastatic colorectal cancer

Introduction

Colorectal cancer (CRC) remains a major public health problem in the United States and worldwide. In 2018, CRC will be diagnosed in an estimated 140,000 Americans, and nearly 52,000 people in this country will die of the disease.[1] CRC is the third most common cancer diagnosis for both men and women in the United States, and the second leading cause of cancer deaths. Over the past 20 years, significant improvements in screening and early detection, as well as advances in the surgical and systemic treatment of early-stage and metastatic disease, have resulted in a steady decline in CRC-associated mortality.[1] Despite the significant progress made over the past 20 years, especially the development of new cytotoxic agents, biologic agents, targeted therapies, and immunotherapies, the 5-year survival rate for patients with a diagnosis of metastatic disease remains low, at approximately 10%.[2,3] Clearly, more effective treatments are urgently needed for patients with metastatic CRC (mCRC) that is refractory to standard chemotherapy. The therapeutic options for patients with mCRC that progresses beyond first- and second-line therapy remain limited, and they are in large part determined by the patient's previous treatment regimens and overall performance status.

Oral Agents in the Setting of Chemorefractory Disease

Regorafenib (Stivarga, Bayer) and trifluridine/tipiracil, also known as TAS-102 (Lonsurf, Taiho Oncology), are the 2 oral agents currently approved in the United States for third-line use in the setting of chemorefractory disease.[4,5] Regorafenib is an oral small-molecule inhibitor that is active against multiple kinases: the angiogenic receptor tyrosine kinases vascular endothelial growth factor receptor 1 (VEGFR1), VEGFR2, VEGFR3, and TIE2 (also known as TEK); the oncogenic receptor tyrosine kinases c-KIT and RET; the stromal receptor tyrosine kinases platelet-derived growth factor receptor beta (PDGFRB) and fibroblast growth factor receptor 1 (FGFR1); and the intracellular signaling kinases c-RAF/RAF-1, BRAF, and BRAF V600E. This agent was approved in 2012 by the US Food and Drug Administration (FDA) for the treatment of mCRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and (in the presence of wild-type *RAS*) an anti–endothelial growth factor receptor (EGFR) therapy.

CORRECT (Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) was a randomized phase 3 study comparing regorafenib vs placebo in patients with mCRC who had received all standard therapies, and it was the positive results from this pivotal trial that led to FDA approval.[6] Patients randomly assigned to the regorafenib arm showed significant improvement in median overall survival (OS) vs those treated with placebo (6.4 vs 5.0 months; hazard ratio [HR], 0.77; 1-sided P=.0052).[4] The overall response rate with regorafenib was low, at 1%, whereas the disease control rate (partial response + stable disease) was much higher, at 41%. Overall treatment-related adverse events (AEs) were observed in 93% of the patients treated with regorafenib. The most common grade 3 or higher AEs associated with regorafenib therapy were hand-foot syndrome (17%), fatigue (10%), diarrhea (7%), and skin rash (6%).

CONCUR (Asian Subjects with Metastatic Colorectal Cancer Treated with Regorafenib or Placebo after Failure of Standard Therapy) was a confirmatory trial conducted in Asia. This study provided further support for the clinical activity of regorafenib therapy, which improved median OS from 6.3 months (with placebo) to 8.8 months (HR, 0.55; 1-sided P=.00016).[7] As in the

CORRECT trial, a high incidence of AEs was observed with regorafenib (97%). Grade 3 or 4 toxicities were seen in more than 50% of patients, with hand-foot syndrome occurring in 17% of patients.

TAS-102 is an oral fluoropyrimidine analogue that was approved in the United States in 2015 for the treatment of mCRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF biologic product; and an anti-EGFR monoclonal antibody for *RAS* wild-type disease.[5] Trifluridine is a thymidine-based nucleoside analogue that is metabolized to the triphosphate metabolite, which is then incorporated into DNA, resulting in the inhibition of DNA synthesis and function.[8] This DNA-mediated process is felt to be the main mechanism by which TAS-102 exerts its antitumor effects. However, trifluridine triphosphate can also be incorporated into RNA, leading to the inhibition of mRNA translation and processing. The trifluridine monophosphate metabolite inhibits thymidylate synthase (TS), which is the key enzyme that catalyzes the de novo synthesis of thymidylate, an essential nucleotide precursor for DNA biosynthesis. However, the trifluridine monophosphate is a much weaker inhibitor of TS than the 5-fluorouracil (5-FU) metabolite 5-fluorodeoxyuridine monophosphate, and TS inhibition is felt to play a relatively minor role in the antitumor activity of TAS-102 in comparison with 5-FU and capecitabine.[8]

RECOURSE (Study of TAS-102 in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies) was a large, international, randomized phase 3 trial that investigated the clinical efficacy and safety of TAS-102 in patients who had mCRC refractory to standard therapies, or who could not tolerate standard therapies.[9] For this study, patients had to have been treated with at least 2 prior lines of standard chemotherapy, which included fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab (Avastin, Genentech). Patients with *KRAS* wild-type tumors were also required to have previously received an anti-EGFR antibody, either cetuximab (Erbitux, Lilly) or panitumumab (Vectibix, Amgen). TAS-102 therapy significantly improved OS in comparison with placebo (median OS, 7.1 vs 5.3 months; HR, 0.68; *P*<.001). Clinical benefit was also observed; significant improvements were noted in progression-free survival (PFS, 2.0 vs 1.7 months; HR, 0.48; *P* <.001) and the disease control rate, defined as the percentage of patients with a complete response, a partial response, or stable disease (44% vs 16%; *P*<0.001), with TAS-102 vs placebo. It should be noted that the objective response rate (ORR, complete response or partial response) was relatively low, at only 1.6% with TAS-102 vs 0.4% with placebo, and this difference did not reach statistical significance (*P*=.29).

In terms of its safety profile, TAS-102 therapy was associated with a relatively high incidence of grade 3 or higher AEs (69%), with myelosuppression the main dose-limiting toxicity. The incidence of grade 3 or higher neutropenia was 38% in patients treated with TAS-102, although this translated into a relatively low incidence of febrile neutropenia (4%). Compared with placebo, TAS-102 was also associated with a higher incidence of grade 3 or higher anemia (18% vs 3%) and grade 3 or higher thrombocytopenia (5% vs <1%), and with higher rates of grade 3 or higher nausea (2% vs 1%), vomiting (2% vs <1%), and diarrhea (3% vs <1%). In the report of Masuishi and colleagues[10] on the Japanese experience of TAS-102, which closely mirrored that reported in the international RECOURSE study, the median PFS and OS were 2.1 months and 6.7 months, respectively. These researchers also found that the clinical efficacy and safety of TAS-102 did not differ between patients with and those without prior regorafenib therapy.

To date, no clinical studies have directly compared the efficacy and safety of regorafenib and TAS-102 in the setting of chemorefractory mCRC. In place of such a direct comparison, Abrahao and colleagues[11] performed a systematic review of randomized clinical trials and used network meta-analyses methods to add an indirect comparison. This study showed no statistically significant difference in PFS or OS between regorafenib and TAS-102. However, the analysis revealed a statistically significant higher level of all-grade toxicity with regorafenib in comparison with TAS-102. A propensity score analysis of regorafenib vs TAS-102, conducted by Moriwaki and colleagues[12] in Japan, showed similar OS in the 2 treatment groups. A subgroup analysis identified a significant interaction with age, in which regorafenib was associated with favorable survival in patients younger than 65 years and TAS-102 was associated with favorable survival in patients 65 years of age or older.

Immune Checkpoint Therapy in the Setting of Chemorefractory Disease

In the fall of 2017, the FDA approved 2 immune checkpoint inhibitors, pembrolizumab (Keytruda, Merck) and nivolumab (Opdivo, Bristol-Myers Squibb), for the treatment of microsatellite instability–high (MSI-H) or mismatch repair (MMR)–deficient mCRC that had progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. The approval for pembrolizumab was based on the phase 2 study conducted by Le and colleagues,[13] who reported a 40% response rate and a 90% disease control rate in patients with MSI-H mCRC. At the time of their analysis, the median PFS and median OS had not been reached. These results were

impressive because the patients enrolled in this study were heavily pretreated, having received a median of 4 different regimens. In contrast, pembrolizumab showed virtually no clinical activity in patients with MMR-proficient or microsatellite-stable (MSS) disease. With no observed responses to pembrolizumab in these patients, the disease control rate was 11%, the median PFS was 2.2 months, and the median OS was 5 months. Pembrolizumab therapy was relatively well tolerated; the most common grade 3 or 4 AEs were skin rash or pruritus (24%); thyroiditis, hypothyroidism, or hypophysitis (10%); and asymptomatic pancreatitis (15%). Similar results were obtained with single-agent nivolumab in patients who had MMR-deficient or MSI-H mCRC in the phase 2 CheckMate 142 study (An Investigational Immuno-therapy Study of Nivolumab, and Nivolumab in Combination With Other Anti-cancer Drugs, in Colon Cancer That Has Come Back or Has Spread).[14] In this multicenter international study, single-agent therapy with nivolumab was associated with a 31.1% ORR and a 69% disease control rate. Median PFS was 9.6 months, and at the time of analysis, median OS had not been reached. The most common grade 3 or 4 toxicities were elevated serum lipase (8%) and serum amylase (3%).

Single-agent anti–programmed death 1 (PD-1) immune checkpoint therapy does not have clinical activity in the setting of MSS mCRC. However, significant efforts are currently focused on identifying the subset of patients with MSS mCRC who may benefit from treatment regimens that combine immune checkpoint blockade either with other immunotherapies or with inhibitors of key signaling pathways. As one example, a phase 1 study investigating the combination of atezolizumab (Tecentriq, Genentech), an anti–programmed death ligand 1 (PD-L1) antibody, and cobimetinib (Cotellic, Genentech), a MEK inhibitor, in MSS mCRC has reported a promising overall response rate of nearly 20%.[15] These encouraging clinical findings provided the rationale for the pivotal phase 3 trial testing the dual combination of atezolizumab and cobimetinib vs atezolizumab monotherapy vs regorafenib monotherapy; this trial has completed patient enrollment and is now awaiting analysis.

Immune checkpoint therapy with pembrolizumab or nivolumab has clear benefit in MSI-H/MMR-deficient mCRC and should be considered an appropriate treatment option in this setting, whereas there is currently no evidence to suggest the use of these immune checkpoint agents as monotherapy in the setting of MSS mCRC. However, they are being combined with other immune-based therapies and/or with various targeted agents for MSS mCRC in early-phase clinical trials, and the results of these studies are eagerly awaited.

Molecular Profiling

Molecular profiling of mCRC has become an important approach to help identify potential treatment options for patients with progressive refractory disease. Next-generation sequencing is now the most widely used approach, for several reasons: it is highly sensitive (requiring only small amounts of tumor DNA); includes a large panel of genes; and can detect novel mutations, small insertions and deletions, copy number alterations, and certain gene fusions and rearrangements.[16] Investigators from MD Anderson Cancer Center[17,18] and Memorial Sloan Kettering Cancer Center[19] have been particularly active in developing molecular screening programs for mCRC and other advanced solid tumors that can be used to identify patients for whom enrollment in biomarker-selected clinical trials and/or treatment with known targeted therapies is appropriate. There are several potential actionable mutations in CRC, which include mutations in *EGFR*, *AKT*, *PIK3CA*, and *MAP2K1* and amplification in the *MET* and *FGFR* genes.[20] In addition, inhibitors that target poly(adenosine diphosphate-ribose) polymerase (PARP) may be active in the setting of *BRCA1/2* mutations or in the setting of alterations in other DNA damage response proteins, such as the ataxia-telangiectasia mutated (ATM) and ataxia-telangiectasia and Rad3-related (ATR) proteins.

Amplification of the human epidermal growth factor receptor 2 gene (*HER2*) is present in nearly 5% of cases of mCRC, whereas mutations in the *HER2* gene are present in only 1% to 2% of cases.[20,21] Several HER2-directed treatment strategies have been or are being evaluated in mCRC. HERACLES (HER2 Amplification for Colorectal Cancer Enhanced Stratification) was the first large phase 2 clinical trial to evaluate the tyrosine kinase inhibitor lapatinib (Tykerb, Novartis) in combination with the HER2-targeted monoclonal antibody trastuzumab (Herceptin, Genentech) in patients with *HER2*-amplified mCRC. HER2 positivity was defined as a score of 2+ or 3+ by immunohistochemistry or as fluorescence in situ hybridization positivity. In this study, the response rate of patients who had *HER2*-amplified mCRC refractory to standard therapy, including anti-EGFR antibodies, and were treated with lapatinib plus trastuzumab was 30%, with a median duration of response of nearly 9 months and a median PFS of 4.9 months.[22]

The HERACLES-RESCUE trial is a follow-up to the initial HERACLES trial in which the role of the antibody-drug conjugate ado-trastuzumab emtansine (T-DM1; Kadcyla, Genentech) in patients with progression on the trastuzumab and lapatinib combination is being investigated.[23] MyPathway (A Study Evaluating Herceptin/Perjeta, Tarceva, Zelboraf/Cotellic, Erivedge,

Alecensa, and Tecentriq Treatment Targeted Against Certain Mutations in Participants With Advanced Solid Tumors; NCT02091141) is a genome-driven clinical trial testing the dual combination of trastuzumab and pertuzumab (Perjeta, Genentech) in *HER2*-amplified and *HER2*-mutated tumors.[24] To date, the interim efficacy data from MyPathway, reported by Hurwitz and colleagues, appear to be similar to the findings in HERACLES, with a 38% ORR, a 10.3-month median duration of response, and a median PFS of 4.6 months.[24] Of note, none of the 9 patients with mutant *KRAS* and *HER2*-amplified/overexpressed mCRC responded to trastuzumab/pertuzumab.

Investigators from the UCSF Helen Diller Family Comprehensive Cancer Center reported their experience with T-DM1 in a patient with *HER2*-amplified, rapidly progressive mCRC.[25] This patient's disease had rapidly progressed on 2 previous treatment regimens that combined cytotoxic chemotherapy with biologic agents. Next-generation sequencing of the primary tumor identified *HER2* amplification. The patient received T-DM1 off label and experienced clinical benefit, with control of his disease for 7 months.

Other possibilities for patients with alterations in *HER2* include enrollment in an ongoing basket trial, such as NCI-MATCH (National Cancer Institute-Molecular Analysis for Therapy Choice), which is testing T-DM1 in *HER2*-amplified cancers, and treatment with afatinib, an irreversible tyrosine kinase inhibitor targeting HER2, EGFR, and HER4 in *HER2*-mutated cancers.

Patient Cases

Case Presentation No. 1

A 70-year-old man presented with mCRC characterized by multiple (<10) small metastases in the liver and lungs. The primary tumor was intact in the sigmoid region. The patient had a long-standing history of hypertension, which was only moderately well controlled, and adult-onset diabetes mellitus. He also had chronic atrial fibrillation, for which he took the calcium channel blocker diltiazem and the oral anticoagulant warfarin. He had no prior history of bleeding or arterio-embolic events. An assessment of one of the liver lesions revealed wild-type *KRAS*, *NRAS*, and *BRAF*.

After the patient had received 5-FU, leucovorin, and oxaliplatin (mFOLFOX6) plus bevacizumab as first-line therapy for nearly 11 months, disease progression with new liver lesions and retroperitoneal adenopathy was observed. The patient was experiencing new symptoms of right upper quadrant abdominal pain, which interfered with his normal activities of daily living. His Eastern Cooperative Oncology Group (ECOG) performance sta-

tus was 1 (PS1). After treatment with 5-FU, leucovorin, and irinotecan (FOLFIRI) plus cetuximab as second-line therapy for 6 months, follow-up computed tomography revealed progressive disease in the lungs.

Currently, the patient's overall performance status remains good (PS1), although he is easily fatigued with increasing dyspnea on exertion. He takes lisinopril for his hypertension and remains on oral warfarin. His liver function tests show mildly elevated aspartate aminotransferase (AST; 90 U/L) and alanine aminotransferase (ALT; 100 U/L) as well as increased serum bilirubin (2.0 mg/dL). His carcinoembryonic antigen (CEA) level has risen from 115 to 375 ng/mL. The rest of his laboratory blood work is unremarkable.

Question: Which one of the following treatments would be most appropriate in this patient?

A. Regorafenib
B. TAS-102
C. Infusional 5-FU
D. Bevacizumab
E. Phase 1 clinical trial

Answer: The most appropriate treatment for this patient is TAS-102 (option B). He has previously been treated with infusional 5-FU in both the first- and second-line settings. His disease is clearly resistant to infusional 5-FU combination therapy, so it is unlikely that any meaningful response would be observed with infusional 5-FU monotherapy. The same would hold for oral capecitabine, given that capecitabine closely mimics infusional 5-FU from a pharmacologic perspective. Currently, no data support the use of single-agent bevacizumab in this setting. A clinical trial is always an appropriate treatment option in patients with refractory disease who continue to have a good performance status, as this patient does. However, this patient has impaired hepatic function, with elevated AST and ALT levels and an increased serum bilirubin level, which would normally exclude him from a phase 1 clinical trial. Enrollment in a genome-driven trial could be considered as a treatment option, but under ideal circumstances, this would require an updated molecular analysis of one of his recent metastatic lesions. Unfortunately, the only genetic data for his disease are those obtained at the time of his initial presentation, and it is conceivable that new molecular alterations have emerged with disease progression.

Regorafenib and TAS-102 are appropriate treatment options for this patient, who has chemorefractory disease. However, there are several concerns regarding the use of regorafenib in this case. First, regorafenib is metabolized by the hepatic cytochrome P450 3A4 (CYP3A4) system,

and as a result, important drug-drug interactions occur with several other agents metabolized by the CYP3A4 system, including warfarin and diltiazem. Although long-term anticoagulant therapy is not a contraindication to regorafenib, more careful monitoring of the coagulation parameters is required. Second, impaired hepatic function is already evident, presumably secondary to the patient's underlying disease. Hepatotoxicity is a black box warning associated with regorafenib therapy, so it would be prudent to avoid using regorafenib at this time. Third, a propensity analysis conducted in Japan suggested that patients younger than 65 years derive greater clinical benefit from regorafenib, whereas those older than 65 years appear to derive greater clinical benefit from TAS-102. This patient is 70 years old, so the expectation would be that he would derive greater clinical benefit from TAS-102 therapy. Finally, fatigue can be a significant issue in some patients taking regorafenib. Given that this patient is already experiencing baseline fatigue, it would probably best to avoid regorafenib therapy. TAS-102 would be the best option for him, given that no dose adjustments are needed for patients with underlying hepatic dysfunction and the agent is not associated with hepatotoxicity. The main dose-limiting toxicity is myelosuppression with neutropenia, and although fatigue can be observed, this side effect occurs much less frequently than with regorafenib. In addition, one does not need to be concerned about the various drug-drug interactions that are typically associated with regorafenib. My own clinical experience has been that patients tolerate TAS-102 much more easily, especially older patients. In some cases, disease control can be prolonged, extending for 12 months or longer.

Case Presentation No. 2

A 68-year-old woman presented with multiple new liver metastases, deemed to be surgically unresectable, and an elevated CEA level of 40 ng/mL. Her medical history was significant only for hypertension, which was well controlled with a thiazide diuretic. Molecular analysis of one of the liver lesions revealed wild-type *KRAS*, *NRAS*, and *BRAF*, with intact MMR proteins.

The patient was treated initially with FOLFOX plus bevacizumab, and 4 months later, interval computed tomography showed a nice response—regression in the size of most of the liver lesions. Treatment was continued, and after 10 months of therapy, progressive disease was detected, with multiple new lesions in the liver and the appearance of new lesions in both lung fields. The patient was then switched to a second-line regimen of FOL-FIRI, and bevacizumab was continued. This treatment was continued for 4 months, with a modest reduction in the size of her lung lesions and stable disease in the

liver. Subsequent imaging 2 months later revealed disease progression in the liver along with increasing right upper quadrant abdominal pain. Her CEA level at the time of progression was 125 ng/mL. A biopsy specimen of one of the enlarging liver lesions was obtained, and molecular analysis with next-generation sequencing revealed wild-type *KRAS*, *NRAS*, and *BRAF*; intact MMR proteins; and *HER2* gene amplification but no mutations in *HER2* or any of the other *HER* gene family members. Further testing of the tumor tissue by immunohistochemistry revealed 3+ staining for the HER2 protein. Currently, the patient feels well overall, except for mild fatigue and pain in the right upper quadrant of the abdomen (PS1). Her serum chemistries, including liver function tests, and complete blood cell (CBC) count are normal.

Question: Which one of the following treatments would be most appropriate in this patient?

A. Regorafenib
B. TAS-102
C. Trastuzumab and lapatinib
D. Afatinib
E. Pembrolizumab

Answer: Based on the results of the HERACLES study, the most appropriate treatment option for this patient is the combination of trastuzumab and lapatinib (option C), provided that these agents can be obtained for off-label use. The presence of *HER2* amplification in one of the metastatic liver lesions justifies this treatment. Afatinib is a small-molecule inhibitor that targets EGFR, HER2, and HER4, but it would not be an appropriate option for this patient because the molecular analysis did not reveal the presence of *EGFR*, *HER2*, and *HER4* mutations in the tumor tissue.

Regorafenib and TAS-102 are certainly reasonable treatment options for this patient, but only after disease progression on therapies that directly target the *HER2* amplification.

Pembrolizumab would not be an appropriate treatment option because molecular analysis of her metastatic disease revealed intact MMR proteins. As such, pembrolizumab monotherapy would not be expected to have any clinical activity.

Disclosure
Dr Chu does not have any relevant financial disclosures.

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