cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

Colorectal Cancer Liver Metastasis: Evolving Paradigms and Future Directions

Luai R. Zarour,[1] Sudarshan Anand,[2,3] Kevin G. Billingsley,[1,3] William H. Bisson,[3,4] Andrea Cercek,[5] Michael F. Clarke,[6,7] Lisa M. Coussens,[2,3] Charles E. Gast,[2] Cristina B. Geltzeiler,[8] Lissi Hansen,[3,9] Katherine A. Kelley,[8] Charles D. Lopez,[3,10] Shushan R. Rana,[11] Rebecca Ruhl,[2] V. Liana Tsikitis,[3,8] Gina M. Vaccaro,[3,10] Melissa H. Wong,[2,3] and Skye C. Mayo[1,3]

[1]Division of Surgical Oncology, [8]Division of Colorectal Surgery, Department of Surgery, [2]Department of Cell Developmental and Cancer Biology, [3]The Knight Cancer Institute, [9]School of Nursing, [10]Division of Hematology and Medical Oncology, Department of Medicine, [11]Department of Radiation Medicine, Oregon Heath and Science University, Portland, Oregon; [4]Environmental and Molecular Toxicology, Oregon State University, Corvallis, Oregon; [5]Department of Gastrointestinal Medical Oncology, Solid Tumor Division, Memorial Sloan-Kettering Cancer Center, New York, New York; [6]Stanford Institute for Stem Cell and Regenerative Medicine, [7]Division of Oncology, Department of Medicine, Stanford University, Stanford, California

SUMMARY

Colorectal cancer ranks as the second leading cause of cancer-related deaths, with metastatic disease to the liver a common cause. Here we discuss exciting developments in the field that promise innovative approaches for early detection and treatment of metastatic colorectal cancer in the liver.

In patients with colorectal cancer (CRC) that metastasizes to the liver, there are several key goals for improving outcomes including early detection, effective prognostic indicators of treatment response, and accurate identification of patients at high risk for recurrence. Although new therapeutic regimens developed over the past decade have increased survival, there is substantial room for improvement in selecting targeted treatment regimens for the patients who will derive the most benefit. Recently, there have been exciting developments in identifying high-risk patient cohorts, refinements in the understanding of systemic vs localized drug delivery to metastatic niches, liquid biomarker development, and dramatic advances in tumor immune therapy, all of which promise new and innovative approaches to tackling the problem of detecting and treating the metastatic spread of CRC to the liver. Our multidisciplinary group held a state-of-the-science symposium this past year to review advances in this rapidly evolving field. Herein, we present a discussion around the issues facing treatment of patients with CRC liver metastases, including the relationship of discrete gene signatures with prognosis. We also discuss the latest advances to maximize regional and systemic therapies aimed at decreasing intrahepatic recurrence, review recent insights into the tumor microenvironment, and summarize advances in noninvasive multimodal biomarkers for early detection of primary and recurrent disease. As we continue to advance clinically and technologically in the field of colorectal tumor biology, our goal should be continued refinement of predictive and prognostic studies to decrease recurrence after curative resection and minimize treatment toxicity to patients through a tailored multidisciplinary approach to cancer care. ***(Cell Mol Gastroenterol Hepatol 2017;3:163–173; http://dx.doi.org/10.1016/j.jcmgh.2017.01.006)***

Keywords: Colorectal Cancer Liver Metastasis; Biomarkers; Hepatic Arterial Infusion; High-Risk Colorectal Cancer; Recurrence.

Colorectal cancer (CRC) is the third most common cancer worldwide, ranking as high as the second leading cause of cancer-related deaths in developed countries.[1–3] The liver is recognized as the most common site of CRC metastasis because the majority of the intestinal mesenteric drainage enters the hepatic portal venous system. More than 50% of patients with CRC will develop metastatic disease to their liver over the course of their life, which ultimately results in death for more than two thirds of these patients.[4,5] Currently, hepatic resection of colorectal cancer liver metastasis (CRLM) in patients with isolated

Abbreviations used in this paper: **CDX2, caudal-type homeobox transcription factor 2; CEA, carcinoembryonic antigen; cfDNA, cell-free DNA; CK, cytokeratin; CRC, colorectal cancer; CRLM, colorectal cancer liver metastasis; CTC, circulating tumor cells; DFS, disease-free survival; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; 5-FU, fluorouracil; HAI, hepatic arterial infusion; IL, interleukin; LV, leucovorin; miRNA, microRNA; MSI, microsatellite instability; OS, overall survival; PD, programmed death; T_H, T-helper.**

Most current article

2352-345X
http://dx.doi.org/10.1016/j.jcmgh.2017.01.006

liver metastasis remains the only option for potential cure. However, even when resection is combined with modern adjuvant systemic regimens, it is curative in only 20% of patients,[4–6] with 70% developing recurrence, primarily in the liver.[4] Efforts to prevent recurrence are limited by the cumulative side effects of systemic therapy, development of chemoresistant cancer clones, and the inability to detect progression of radiographically occult micrometastatic disease. In an updated analysis of a large randomized controlled trial that examined the role of perioperative systemic therapy in patients with resectable CRLM before and after curative hepatic resection, there was no improvement in 5-year overall survival (OS) compared with patients treated with hepatic resection alone (51% vs 48%; $P = .34$).[7,8] Although perioperative systemic therapy remains the standard of care for patients with resected CRLM, there is significant opportunity to identify patients more accurately with a molecular high-risk signature who will benefit from adjuvant treatment aimed to decrease intrahepatic recurrence.[9] In addition, for patients with liver-only metastatic CRC treated with curative intent surgery, detecting disease recurrence at the earliest stage and monitoring response to treatment are paramount to moving the field forward. In this report, we review modern approaches for treating patients with CRLM and ongoing work to optimize molecular risk stratification to direct systemic treatment and to monitor for intrahepatic recurrence (Figure 1).

Scope of the Clinical Problem for Patients With Colorectal Cancer Liver Metastasis

Detecting primary CRC and CRLM at an early stage results in better outcomes.[10] At a molecular level, CRC consists of a heterogeneous group of diseases with molecularly, as well as clinically, distinct tumors based on the primary site of origin (eg, colon vs rectal, and right-sided vs left-sided). Chromosomal instability, deficient mismatch repair (dMMR) with resultant microsatellite instability (MSI), aberrant DNA methylation,[11] as well as altered molecular signaling pathways all have been described in the transformation from normal mucosa to adenocarcinoma.[12–16] The role of biologics in the adjuvant treatment of resected primary CRC has been evaluated, including cetuximab for Kirsten rat sarcoma viral oncogene (KRAS) wild-type cancers and the vascular endothelial growth factor inhibitor bevacizumab; however, these targeted treatments have not shown the benefit seen in the metastatic or advanced setting.[17–19] More recently, those altered pathways and mutations have been used for therapy modification and patient stratification in metastatic CRC based on the sidedness of the primary tumor, supporting the use of different biologic agents for distinct primary biology underlying the disease.[17–19] Chromosomal anomalies with demonstrated importance in tumorigenesis, including DNA gains or losses, result in changes in gene expressions that might lead to a differential response to chemotherapeutic agents. This recently was studied in an analysis of cell-free DNA (cfDNA) showing acquired resistance to anti–epidermal growth factor (EGFR) therapies,[20] as well as recent investigations reporting a correlation between DNA copy number losses and an association with response to fluorouracil (5-FU), irinotecan, and capecitabine.[21]

Given the extensive molecular and clinical heterogeneity of CRC, it is essential to individualize therapy on the basis of molecular profiling to avoid treatment-related toxicities without a realized survival benefit. Some of the strongest data to support the need for identification of high-risk cohorts among patients with CRLM come from adjuvant trials for primary CRC. The 2004 adjuvant the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial[22] assessed the impact of an oxaliplatin-containing systemic regimen (folinic acid, 5-FU, and oxaliplatin) for patients with resected primary CRC compared with 5-FU alone in patients with stage II and III disease. A significant survival benefit for patients with stage III disease was found and has been maintained in recently updated 10-year results.[23] However, these benefits come with significant morbidity impacting patient quality of life. For patients with stage III CRC treated with folinic acid, 5-FU, and oxaliplatin, instead of 5-FU and leucovorin (LV), there is a consequent 4% decrease in mortality.[23] However, to achieve this 4% reduction in mortality with oxaliplatin, 92% of those patients will suffer from treatment-associated peripheral neuropathy, with approximately 15% experiencing permanent neuropathy when followed up longitudinally for 2 years.[24] It is clear that even among patients with stage III disease there is an underappreciated disease heterogeneity that at present is being treated with an often-homogenous systemic approach. These data in the primary CRC setting underscore the need for molecularly driven systemic treatment to avoid both the financial and quality-of-life costs to patients with liver-only metastatic CRC. Work is ongoing to identify molecular subsets of patients with CRLM to personalize targeted treatments to maximize therapeutic interventions. In this review, we describe the role of liquid biopsies (ie, analyses of tumor cells or tumor derived material that is circulating in the blood) along with novel cancer and immunologic cell populations to both surveil and assess treatment response in patients with CRLM. We also propose using this information to guide the design and development of therapeutic strategies for liver-directed treatments.

Treatment Challenges for Patients With Liver-Only Metastases

For patients with liver-only metastatic CRC, there is a pressing need for a more robust molecular characterization of the primary and metastatic lesions to direct perioperative management of patients at highest risk for disease recurrence.[25] In the primary disease setting, the focus has been directed toward patients with high-risk stage II CRC—those patients with negative lymph nodes but other high-risk features such as T4 lesions, obstruction or perforation, cancers with lymphovascular invasion, and poorly differentiated histology. One of the early investigations on the