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Personalized treatment in patients with colorectal liver metastases

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ARTICLE INFO

Article history:
Received 19 January 2017
Received in revised form
19 February 2017
Accepted 11 April 2017
Available online 20 April 2017

Keywords:
Colorectal liver metastases
Personalized medicine
Treatment

ABSTRACT

Background: Precision Medicine Initiative is a new research effort aiming to offer personalized treatment in many diseases, including cancer. The aim of the present article is to offer novel insights about the role of personalized treatment in patients with colorectal liver metastases (CRLM).

Methods: A review of the literature regarding personalized medicine and colorectal liver metastases was performed mainly in the MEDLINE/PubMed database.

Results: Surgical resection remains the only hope for cure of CRLM. Improved surgical strategies to optimize remnant liver volume are recently introduced and gaining ground. Following resection of CRLM scoring systems have been developed by combining certain preoperative factors such as microsatellite instability KRAS expression and sensitivity to immunotherapy with Programmed Death-1 inhibitor.

Conclusions: Multidisciplinary management of patients with CRLM has markedly contributed to increased survival. While the last several decades have been characterized by these important developments, future advances for patients with CRLM will depend on a better understanding of genomics and molecular biology to facilitate characterization of a specific tumor "identity" so that individualized treatment for each CRLM patient becomes the rule, and not the exception.

On January 20, 2015, President Obama announced the Precision Medicine Initiative, a new research effort that has the potential to revolutionize how we treat disease, including cancer. Genetic and molecular profiling of tumor specimens have revealed potential targets for personalized anticancer therapy and seen a shift toward an emerging molecular taxonomy of cancer.[1] Genomics and molecular biology are providing unprecedented opportunities to uncover the underlying genetic pathways driving cancer and are accelerating the development of personalized treatment strategies. Like many cancers, colorectal liver metastasis (CRLM) is an extraordinarily heterogeneous malignant disease probably due to variabilities in genomic profile, molecular and signal transduction network, and microenvironment discrepancies.[2] Multidisciplinary approach for liver metastases currently represents the best strategy in the management of patients with colorectal cancer.

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0022-4804/$ – see front matter
http://dx.doi.org/10.1016/j.jss.2017.04.013

The role of surgery in CRLM patients

Surgical resection remains the only hope for cure of CRLM. Although surgery is associated with a low-operative mortality of 1%-2%,[3] long-term survival is variable depending on the era from which the data are reported and the underlying patient population.[4] R0 resection, combined with modern systemic therapy, remains the cornerstone for increasing 5-year survival that now approaches 50%-60%.[5] Improved surgical strategies to optimize remnant liver volume such as portal vein embolization (PVE), two-stage hepatectomy, Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy, and the widespread adoption of parenchymal sparing resection have allowed hepatectomy to be offered to more patients who have a greater tumor burden and more widespread disease.[6-8] Despite this, many patients are not candidates for resection due to clinical and/or technical reasons (severe comorbidities, extensive intrahepatic multifocal disease, unresectable extrahepatic disease, and so forth).[9] In addition, even among patients resected for cure, disease recurrence occurs in up to 70% of patients, most often during the first 3 y after surgery.[4] When recurrence is intrahepatic only, repeat hepatic resection may be feasible, however "true" long-term cure remains difficult to achieve.[8]

Predictive models in CRLM patients

Following resection of CRLM, morphologic criteria are typically used to predict which patients have more aggressive disease and are, therefore, more likely to experience recurrence and have worse long-term survival. Scoring systems based on these clinicopathological factors historically have included preoperative factors such as primary tumor stage, carcinoembryonic antigen levels, number of liver metastases, presence of extrahepatic disease, as well as other factors.[10] Although scoring systems have been developed by combining certain preoperative factors, these have been inconsistent in accurately determining prognosis. Microsatellite instability (MSI) is considered a promising factor that could potentially enable identification of patients who may benefit from the chemotherapy and, in particular, immunotherapy with PD-1 inhibitor therapy.[11] The predictive value of the MSI status in palliative treatment remains, however, controversial.[12]

Moreover, there is a growing body of data published about the role of genomic and molecular biomarkers to predict prognosis following CRLM.[13] The clinical impact of Kirsten ras (KRAS) mutation status among patients with CRLM has garnered considerable interest with data from clinical trials noting its potential role as prognostic biomarker.[14] A recent meta-analysis suggested that KRAS mutations were prognostic biomarkers associated with worse survival outcomes among CRLM patients undergoing hepatic resection.[15] Our group has demonstrated that KRAS G12V and G12S mutations of codon 12 were independent prognostic factors of worse overall survival.[16] In a separate study, KAS codon 13 mutations, but not codon 12 mutations, were associated with a higher risk for overall extrahepatic recurrence and lung-specific recurrence.[17] As such, information on specific KRAS mutations may help individualize therapeutic and surveillance strategies for patients with resected CRLM. The optimal tumor-free margin width may even be affected by the underlying tumor biology. For example, although a 1- to 4-mm margin clearance in patients with wild type kirsten ras tumors was associated with improved survival, wider resection width did not confer an additional survival benefit. In contrast, margin status, including a 1-cm margin, did not improve survival among patients with mutKRAS tumors.[18] In fact, an R0 margin only provided a survival benefit to patients with wild type kirsten ras tumors. Tumor biology and not surgical technique determined prognosis.[19]

Patients with CRLM are treated with 5-fluorouracil–based chemotherapy commonly combined with oxaliplatin (FOLFOX) and/or irinotecan (FOLFIRI), as well as possibly targeted agents (i.e., bevacizumab, cetuximab, panitumumab, aflibercept, ramucirumab, or regorafenib). Response rates with fluorouracil-based regimens for metastatic disease range from 25%-50%.[20] Currently, choice of systemic therapy for CLRM is largely "generally applied" with either FOLFOX or FOLFIRI based somewhat on patient comorbidities (e.g., diabetes, preexisting neuropathy, and so forth) or anticipated toxicity. More "personalized" application of therapy is much more limited (i.e., KRAS status for cetuximab, and so forth) and still emerging (i.e., possible PD1 therapy for MSI high patients).

Obstacles in the application personalized medicine in CRLM patients

Further improvements in outcomes among patients with CRLM will require increased individualization and personalized treatment of patients with CRLM in a multidisciplinary setting (Fig. 1). In fact, surgical oncology is more personalized

Fig. 1 – Personalized treatment of patients with CRLM in a multidisciplinary setting. (Color version of figure is available online.)