Rationale for Neoadjuvant Chemotherapy of Resectable Colorectal Cancer Liver Metastases: When is it Useful?

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ABSTRACT

Colorectal cancer is the third most common cancer and the third leading cause of cancer death in the United States (1). Moreover, approximately 20% of patients are diagnosed with synchronous colorectal liver metastases (CRLMs)(2). For patients with CRLM, the 5-year survival rate with after chemotherapy alone is approximately 11 percent (3). However, the 5-year and 10-year survival rates after surgical resection are reported as 38% and 26%, respectively (4). Therefore, surgery is considered a potentially curative intervention in CRLM. Unfortunately, not all CRLM patients are candidate for liver resection due to several factors. These include medical comorbidities and anatomical factors such as the number of metastases, tumor size and margin. In some cases, chemotherapy for unresectable tumors could convert the tumors to resectable. In other cases, neoadjuvant chemotherapy can help patients with synchronous metastatic disease undergo performed staged resection. Although neoadjuvant chemotherapy could be useful, its implementation is not yet standard and its use in resectable CRLM remains controversial. This review article focuses on the potential utility of neoadjuvant therapy for CRLMs.

Key words: colorectal cancer, liver metastases, neoadjuvant chemotherapy, resection, immune checkpoint blockade

RATIONALE FOR LIVER METASTASES RESECTION

Which CRLMs are considered “resectable”?

Surgical resection is widely regarded as the best intervention to cure and/or achieve long-term survival in CRLM patients. Since liver resection is major surgery, patients must be selected carefully by taking into consideration factors related to patients' fitness, to the tumors and to their anatomy. Comorbidities, such as other liver diseases, cardiovascular diseases and pulmonary diseases, age and past medical histories can be important risk factors. Factors related to the tumors include established prognostic scoring systems which also evaluate the benefit of neoadjuvant chemotherapy for CRLMs (5-12). The major compo-

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nents in these scoring systems are the size of the largest metastatic lesion, the number of metastases, margin, bilobar liver disease, N and T status, differentiation of primary tumor, CEA level, presence of resectable extra-hepatic disease, and interval after primary or liver metastasis. Although few of these scoring systems could predict survival more than 5 years, these scoring are often used for treatment decisions (13). For patients with CRLM who require major liver resection, staged surgery with complementary procedures, such as the portal vein embolization (PVE) (14,15) and the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS)(16, 17), could be considered. Finally, regarding the anatomic factors, major limitations for resection could be the number of CRLMs, tumor size, and their location and margins. The continuous progress in the development of neoadjuvant chemotherapy and surgical procedure has simplified the criteria for resectability (18,19).

How about metachronous CRLMs?

Metachronous CRLMs are liver metastases detected after curative surgery of a primary colorectal cancer. The surgical procedure for treating metachronous CRLM is largely similar to the one used for other liver tumors. If an R0 resection is successfully performed for metachronous CRLMs, the 3-year survival and 5-year survival rates after liver resection are reported as 58% and 42%, respectively (4). To estimate the efficacy of neoadjuvant chemotherapy over surgery first, Adam et al analyzed 1,471 patients with solitary and metachronous CRLMs; of these, 169 patients were treated with at least 3 cycles of an oxaliplatin - or irinotecan-based regimen before surgery while 1,302 patients received no preoperative chemotherapy (20). They reported that preoperative chemotherapy did not improve the disease-free survival (DFS) or overall survival (OS) in these patients with CRLMs of less than 5 cm in size. Thus, the benefit of neoadjuvant chemotherapy remains unclear if the metachronous CRLMs are few, small and easy to resect. However, if the metastatic lesions are multiple or bulky, neoadjuvant chemotherapy may be considered to reduce the burden and the risk of early recurrence after surgery for CRLM, as discussed below.

What is the rationale for using neoadjuvant chemotherapy?

Multiple chemotherapy regimens that include biologics have shown efficacy in metastatic colorectal

cancer (mCRC) patients. Some of these regimens have been tested as neoadjuvant chemotherapies for CRLMs, their role and the optimal regimen are still unclear. Because of the potential resistance and/or toxicity to these drugs, the benefit for neoadjuvant chemotherapy for patients with low risk, few and small tumors is questionable. On the other hand, for patients with high risk, unresectable or borderline resectable, neoadjuvant chemotherapy is considered as an appropriate option. Once neoadjuvant chemotherapy is initiated, it is recommended that the CRLM patients are followed by radiographic examination every 6-8 weeks. To evaluate the effect of the regimen, the RECIST criteria are commonly used (21). CRLMs resection should be performed as soon as possible after tumors are deemed resectable, but at least 4 weeks after finishing chemotherapy (or even longer if the antiangiogenic drug bevacizumab is used) to avoid surgical complications.

STANDARD REGIMENS FOR METASTATIC COLORECTAL CANCER

The regimens that have shown efficacy in randomized phase III clinical trials for mCRC are multiple and include doublet or triplet chemotherapies with biologics. Fluorouracil (FU) and leucovorin (LV) are being combined with oxaliplatin or irinotecan or both, regimens referred to as FOLFOX (22), FOLFIRI (23,24) and FOLFOXIRI (25-27), respectively. There are also modified options for these regimens (using oral capecitabine (28,29) or S-1 (30,31) instead of FU and LV) that have also shown efficacy in randomized trials. In addition, several molecularly targeted drugs have shown efficacy. These include antiangiogenic (anti-vascular endothelial growth factor (VEGF) pathway) drugs such bevacizumab (anti-VEGF antibody)(32-34), aflibercept (chimeric soluble VEGF receptor (VEGFR)-1 or "VEGF-trap")(35), ramucirumab (anti-VEGFR2 antibody)(36) and regorafenib (multikinase inhibitor of VEGFRs and RAF)(37), or tumor-targeted drugs such as anti-epithelial growth factor receptor (EGFR) antibodies (cetuximab and panitumumab) (38-40). Cetuximab and panitumumab are only used for patients with wild-type RAS/BRAF status, because these tumors are invariably resistant to EGFR blockade. Moreover, an analysis of six randomized trials of EGFR antibodies showed a better outcome of this intervention for patients with left-sided CRCs than right-sided CRCs (41). This study showed that tumor sidedness could be one of the critical factors for selecting treatment regimens. TAS-102, an oral drug consisting of trifluridine and tipiracil hydrochloride, has also become a treatment

option for mCRC (42). Finally, while immunotherapy with immune checkpoint blockers has failed to show substantial activity so far in mCRC, blockade of programmed cell death receptor (PD)-1 and cytotoxic T lymphocyte associated protein (CTLA)-4 may be an efficacious option for CRC patients with tumors with deficiencies in mismatch repair (dMMR) or high levels of microsatellite instability (MSI-H); this includes the anti-PD-1 antibody nivolumab with or without the anti-CTLA-4 antibody ipilimumab (43). In this study, overall response rate was 55%, and progression-free survival rates were 76% at 9 months and 71% at 1 year. The promising data from the limited experience with immune checkpoint inhibitors in mCRC needs to be validated in larger trials, and its role in other stages of the disease (for example in neoadjuvant setting) remains to be established.

LIVER TOXICITIES CAUSED BY CHEMOTHERAPY OR BIOLOGICS

In considering neoadjuvant treatment for CRLM, an important factor is the characteristic liver toxicity of the drugs, which could pose a risk for liver resection (44, 45). Oxaliplatin causes sinusoidal obstruction syndrome, which is similar to a venous occlusive disease. Non-cirrhotic portal hypertension has also been reported for the use of oxaliplatin with fluorouracil (45). Irinotecan can cause steatosis and steatohepatitis – adverse effects which correlate with high mortality (46). A more recent report on liver toxicity after preoperative chemotherapy shows that steatohepatitis was observed more frequently after irinotecan than after oxaliplatin (14.8% vs 3.4%) and in patients with body mass index (BMI) > 25 kg/m² (OR= 10.0)(47). Another paper shows that the preoperative aspartate amino-transferase-to-platelet ratio index can predict liver-related complications after neoadjuvant chemotherapy and is related to sinusoidal obstruction syndrome (48). Bevacizumab is often used with oxaliplatin or irinotecan regimen. However, bevacizumab can cause adverse effects such as thromboembolic disease, bleeding and bowel perforation. In addition, it may also cause delays in wound and liver healing post-surgery (49). Therefore, liver resection is usually planned 6 to 8 weeks after bevacizumab therapy, given its prolonged half-life in blood circulation.

GUIDELINES FOR INITIALLY RESECTABLE CRLMS

In the United States of America, the guidelines set

by the National Comprehensive Cancer Network (NCCN) recommended upfront surgery if the tumors are initially resectable (50). For cases where there are more than 4 metastases, suspicion of portal node metastasis or bilobar disease, neoadjuvant chemotherapy is preferred prior to surgical resection. Once neoadjuvant chemotherapy starts, it is critically important to check the tumor status every 6 to 8 weeks using radiographic examinations to minimize the number of chemotherapy courses. In some cases, the CRLMs recur in remaining liver rapidly after resection. Most likely, these CRLMs are present at the time of resection and are particularly aggressive. For these cases, two or three cycles of preoperative chemotherapy may be a useful option to determine whether these CRLM patients will derive benefit from surgical intervention or not (51). In the largest study performed to date, the European Organization for Research and Treatment of Cancer (EORTC) investigators tested whether peri-operative chemotherapy can improve survival in CRLM patients over surgery alone (EORTC Intergroup trial 40983). Patients were randomly assigned to receive FOLFOX4 versus surgery upfront (52,53). In this study, 12 weeks of chemotherapy was planned for both pre- and post-operative period. Sixty-seven of 182 patients were included and about 80% of them were resected in both groups. The HR for progression-free survival was 0.79 (p=0.058) in all randomly assigned patients; this corresponded to an increase in median progression-free survival from 11.7 months to 18.7 months with the addition of chemotherapy. This difference was significant in the patients in whom resection was actually achieved after study entry (HR was 0.73, p=0.025). However, after 8.5 years of follow up, there was no significant statistical differences in 5-year overall survival (52,53). Of note, the trial was not powered to detect a difference in overall survival. The study investigators concluded that – while the difference in survival shown in this study was not statistically significant – further evaluation of peri-operative chemotherapy with FOLFOX4 (with or without biologics) is warranted for resectable CRLM. In conclusion, the benefit of neoadjuvant chemotherapy remains controversial for initially resectable CRLMs.

SYSTEMIC NEOADJUVANT THERAPY REGIMENS FOR INITIALLY RESECTABLE CRLMS

Recently, the number of drugs and regimens that showed efficacy for mCRC has been rapidly increasing. The suggestions included in the NCCN and European

Society for Medical Oncology (ESMO) guidelines for initially resectable CRLMs include the use of FOLFOX, FOLFIRI, XELOX (capecitabine and oxaliplatin) with or without bevacizumab, and FOLFIRI, FOLFOX with or without cetuximab or panitumumab (54). More recently, FOLFOXIRI was also added in the NCCN guideline as a treatment option for neoadjuvant therapy. Adding bevacizumab to the 5-FU and oxaliplatin regimen may improve pathological responses and reduce liver injury (55). Similarly, adding anti-EGFR antibody to chemotherapies can produce “early tumor shrinkage”, and this effect is associated with superior long-term outcomes (56). While these regimens might be useful, there are some critical points that must be kept in mind for choosing regimens. For the use of anti-VEGF as part of neoadjuvant treatment for patients with resectable CRLMs, the concerns are the potential adverse effects of bevacizumab (49). For the use of anti-EGFR therapy, the concerns is the efficacy of the intervention, as the result of the EPOC trial which showed no difference in OS and an inferior progression-free survival (PFS) when cetuximab was added to FOLFOX (57,58).

Potential systemic therapy regimens for unresectable CRLMs

For patients with initially unresectable CRLMs, there is strong rationale for preoperative chemotherapy. Usually patients with initially un-resectable CRLMs receive at least several courses of chemotherapy to evaluate tumor response and reevaluate the resectability. Longer interventions may cause liver damage, which in turn may cause postoperative complications. If neoadjuvant chemotherapy is effective and converts the unresectable CRLMs to resectable, an immediate liver resection is recommended. There ported success rates for conversion after neoadjuvant therapy range between 12-33% (25,59-66). The reported 5-year survival rate after resection are 30-54%, which is considerably higher than that after chemotherapy alone (approximately 10%). After chemotherapy, the rate of complete pathologic response is reported at 4-9% (60,67,68). Even if CRLMs show complete radiologic response after chemotherapy, the vast majority of cases showed persistent macroscopic or microscopic residual disease or early recurrence in situ (69). Thus, resection is strongly indicated even if the CRLMs show complete response by imaging. In these case, identifying tumor locations is critically important; an option to address this problem is using a marking technique consisting of

placing coils using computed tomography or ultrasound guidance before chemotherapy (70).

For initially unresectable CRLMs, all the regimens for unresectable mCRCs are considered appropriate. However, there is no standard regimen for this particular setting. If conversion from initially unresectable or borderline to resectable is expected, there are some recommendations. These include FOLFOX or FOLFOXIRI; for patients with-wild type of RAS and BRAF, FOLFIRI plus cetuximab or panitumumab could also be considered. Since potent cytotoxic regimens are preferred for attempting conversion, doublet therapies which contain either oxaliplatin or irinotecan are usually selected; FOLFOX is more commonly selected than FOLFIRI because irinotecan may cause steatohepatitis. There are some early reports on the use of FOLFOXIRI, which contains both oxaliplatin and irinotecan and appears to be useful for young patients or patients without comorbidities (25,64). From the retrospective analysis of the TRIBE trial, FOLFOXIRI plus bevacizumab may be one of the options for the first-line regimen for patients with right-sided mCRCs regardless of their status of RAS or BRAF mutation, because of their worse prognosis compared to left-sided tumors (71). Finally, while the use of immune checkpoint inhibitors is now standard for unresectable mCRCs with dMMR MSI-H tumors, their safety and utility in neoadjuvant setting remains to be examined.

CONCLUSION

Surgical resection for CRLMs remains the intervention of choice to achieve cure in this advanced disease setting. Although a recent meta-analysis including 18 studies (6,254 patients) shows that neoadjuvant chemotherapy can improve both 5-year DFS (HR 1.38) and 5-year OS (HR=1.19)(72), there are no currently selection criteria for patients and no prospective evidence to prove the benefit of combining targeted agents such as cetuximab and bevacizumab (73). Therefore, for initially resectable CRLMs, resection is usually recommended if feasible. For initially unresectable CRLMs, chemotherapy using cytotoxic regimens should be considered to convert the tumors to resectable. With the advent of multiple effective cytotoxic regimens, biologics and immune checkpoint inhibitors for mCRCs, there are great expectations that new systemic neoadjuvant therapy will further improve the survival outcomes. However, the safety and efficacy of these interventions should be tested and validated in future randomized studies.

Conflict of interest

The authors declare no conflict of interest with this work.

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