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TOPIC HIGHLIGHT

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An update on chemotherapy of colorectal liver metastases

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Abstract

Surgical resection of liver metastases of colorectal cancer greatly improves the clinical outcome of patients with advanced disease. Developments in chemotherapeutic agents and strategies bring hope of a cure to patients with initially unresectable colorectal liver metastases (CLM). Perioperative chemotherapy significantly improves the survival time of patients who receive curative-intent hepatectomy. Even for unresectable CLM, recent studies demonstrated that active preoperative chemotherapy could achieve shrinkage of liver metastasis and thus render some for resection. Furthermore, an increase in tumor resection rate and prolonged survival time among patients with CLM has been observed following the application of monoclonal antibodies in recent years. However, the value of chemotherapy *via* hepatic arterial infusion is still unclear. More trials should be conducted in patients with CLM in order to improve survival.

Key words: Chemotherapy; Colorectal cancer; Liver metastases; Resection rate; Targeted agents

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INTRODUCTION

Colorectal carcinoma is one of the most common causes of cancer-related mortalities in both China and the Western world. Almost 50% of patients with colorectal cancer will eventually develop liver metastases during the natural course of the disease and 25% of patients present with liver metastases at the time of diagnosis. One third of patients with liver metastases have an isolated metastatic site limited to the liver, and the survival of this specific population is directly related to the progression of the hepatic lesions[1]. The management of patients with untreated colorectal liver metastases (CLM) remains a common clinical challenge as previous studies reported a median survival time of 4 mo[2].

The treatment goal for patients with limited CLM is to remove all evidence of disease for better long-term survival or even cure. Historically, only a minority of patients (10%-15%) are considered candidates for resection with overall 5-year survival rates ranging between 25% and 40%[3]. Significant advances have been achieved in the management of CLM in recent years, with improvement in the precision of cross-sectional imaging, surgical techniques, locoregional therapeutic options, and the availability of newer effective chemotherapeutic agents. A multimodality treatment approach for patients with resectable CLM results in more patients being considered for resection and better outcome has been noted, where resectability rate increased to 20%-30%, 5-year survival rate increased to 50%, and 25% of patients survived for not less than 10 years[4,5]. For the time being, although there are still many incurable cases in the most advanced stage, the course of progression can be greatly slowed by multimodality treatment encompassing surgery, chemo-

therapy and interventional locoregional therapy.

Even though surgical resection remains the mainstay of potentially curative therapy, the role of systemic preoperative chemotherapy has been gradually recognized. Standard chemotherapy regimens comprising 5-fluorouracil (5-FU) plus leucovorin (LV) in combination with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) have been reported to facilitate a resection rate of 9%-40% among patients with initially unresectable CLM[6,7]. Perioperative chemotherapy for those with resectable liver lesions confers a potential survival advantage. Moreover, mounting evidence suggests that the addition of targeted agents or a third cytotoxic agent might be even more effective[8].

In this review, we will focus mainly on updates in systemic chemotherapy for CLM, and a short discussion on regional interventional chemotherapy will also be presented.

SYSTEMIC POSTOPERATIVE CHEMOTHERAPY FOR RESECTABLE LIVER METASTASES

Currently, postoperative systemic chemotherapy for resectable CLM, a common practice, carries the same goal as that for stage Ⅲ colorectal cancer to effectively enhance the local disease control rate. However, in contrast to the well-established benefit noted for adjuvant chemotherapy for stage Ⅲ colorectal cancer, there has been few high quality randomized studies to formally evaluate the benefits of adjuvant chemotherapy for CLM, despite the fact that improved survival and reduced recurrence rates have been demonstrated in retrospective studies[9]. In a multicenter, phase Ⅲ Fédération Francophone de la Cancérologie Digestive Association Française de Chirurgie Hépato-Biliaire et de Transplantation Hépatique Association Universitaire de Recherche en Chirurgie (FFCD ACHBTH AURC) 9002 trial, 173 patients who had undergone R0 resection were randomized to surgery followed by bolus 5-FU/LV for 6 mo with interval days of 10-35 or surgery alone[10]. The 5-year disease-free survival (DFS) rates were 33.5% and 26.7% respectively (P = 0.028), suggesting a positive effect of chemotherapy after surgery. There was a trend toward increased 5-year overall survival (OS) in patients who received chemotherapy without statistical significance (51.1% *vs* 41.9%, P = 0.13). The study may have been statistically underpowered to detect a true difference in OS as a result of early termination of accrual due to low accrual rates. An another trial [European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)/Gruppo Interdisciplinare Valutazione Interventi in Oncologia (GIVIO) trial] with a similar design, also closed prematurely due to slow accrual, but showed a trend towards improved progression-free survival (PFS) and OS in the chemotherapy group. Multivariate analysis identified adjuvant chemotherapy as a significant independent prognostic factor even though between-group comparison was insignificant[11]. Some large United States and European retrospective analyses further suggested an urgent need for patients with recurrent disease to receive adjuvant chemotherapy and showed a better survival in resected CLM patients who received adjuvant therapy[12,13].

The choice of regimen is the key to the success of chemotherapy after tumor resection. The 5-FU/LV regimen is less commonly used nowadays, but the efficacy of combining 5-FU with oxaliplatin or irinotecan as postoperative chemotherapy for patients with resectable CLM remains to be elucidated. A randomized phase Ⅲ study comparing adjuvant 5-FU/LV with FOLFIRI in patients following complete resection of CLM reported a median DFS of 24.7 mo and 21.6 mo for FOLFIRI and 5-FU/LV, respectively, with no significant differences noted for DFS and OS, however, a trend in favor of improved DFS in patients treated with FOLFIRI could not be excluded[14]. At present, evidence to support significant additional benefit using combination therapies for resectable CLM has not been established. Thus, the use of postoperative therapy is individualized based on local practice as well-established data from clinical trials are not yet available. The expert panel of the European Colorectal Metastases Treatment Group recommends that systemic chemotherapy following liver resection should be considered as an option for patients with resected CLM, particularly for those patients who did not receive preoperative chemotherapy[8].

PREOPERATIVE CHEMOTHERAPY FOR RESECTABLE CLM

Rising enthusiasm for the role of perioperative chemotherapy in cases of operable carcinoma originating from the digestive system has been noted, including those with CLM. Convincing benefits of preoperative chemotherapy on long-term survival in patients with CLM is still not well-established, but it is gradually being accepted as the rationale to improve PFS and reduce recurrence rates[15]. A ten-year study on survival and recurrence after neoadjuvant chemotherapy followed by resection of liver metastases showed that the 1-, 3- and 5-year OS reached 90%, 59.2% and 46.1%, respectively and DFS at 1, 3 and 5 years was 68.1%, 34.8% and 27.9%, respectively. In addition, preoperative chemotherapy followed by liver metastases resection is associated with improved survival, low cancer involvement in resection margins and re-resection rates[16]. In 2008, Nordlinger *et al*[17] published the final results of the EORTC 40983 study, which compared perioperative chemotherapy with oxaliplatin, fluorouracil, and folinic acid (FOLFOX4) regimen to surgery alone in patients with resectable CLM. Patients were randomly assigned to six cycles of neoadjuvant FOLFOX4 before and after surgery (n = 182) or to surgery alone (n = 182). The 3-year PFS was improved from 28.1% for the surgery-alone group to 36.2% for the perioperative FOLFOX4 group, an increase of 8.1% [hazard ratio (HR) = 0.77; P = 0.041] for all eligible patients and 9.2% (HR = 0.73; P = 0.025) for all resected patients. Additional reports on the application of neoadjuvant chemotherapy came from a few prospective single-center clinical tri-

als[18,19]. In one trial, 50 patients with resectable liver metastases received neoadjuvant capecitabine plus oxaliplatin (XELOX) or FOLFOX4 for six cycles (3 mo) prior to surgical resection[20]. The results suggest that preoperative oxaliplatin-based chemotherapy provides high response rates (RRs) without increased risk of perioperative morbidity. The recurrence-free survival was significantly influenced by tumor response to neoadjuvant chemotherapy, which may identify the best candidates for a potentially curative treatment.

Perioperative chemotherapy with FOLFOX4 may be a possible treatment option for patients with resectable CLM, as prolonged PFS has been noted as mentioned above. Nevertheless, not all patients can be cured *via* surgery with perioperative chemotherapy. 7% of patients in the chemotherapy group in the EORTC 40 983 trial experienced disease progression after receiving 3-4 cycles of chemotherapy. More active regimens should be tried to provide better results[17]. A recent non-randomized trial revealed that the objective response following preoperative chemotherapy of XELOX plus bevacizumab was 73% for a cohort of 56 patients, the treatment being safely administered until 5 wk prior to surgery in patients with resectable CLM without increasing postoperative complications[19]. Liver regeneration was not affected by preoperative bevacizumab. A large randomized clinical trial to evaluate the efficacy of bevacizumab combined with preoperative chemotherapy would better assess the efficacy of this preoperative regimen in patients with resectable CLM. Another study is currently ongoing in Britain to determine if the combination of cetuximab with perioperative chemotherapy could contribute to better survival.

At present time, no mature data is available to support the combination of FOLFOX6, antibodies targeting both vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) in the perioperative setting. Therefore, a large multi-center EORTC 40051 BOS (Biologics, Oxaliplatin and Surgery) trial was launched to evaluate the combination of oxaliplatin-based chemotherapy plus cetuximab with or without bevacizumab in a preoperative (6 cycles) and postoperative (6 cycles) setting in patients with resectable CLM. Patients could have up to ten liver metastases, and up to two pulmonary metastases. The primary endpoints of the BOS trial are preoperative RR and safety. However, based on the disappointing results from the Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) study where the combination of bevacizumab, panitumumab with chemotherapy was first-line therapy for advanced colorectal cancer[20], as well as the discouraging reports from combination chemotherapy with bevacizumab-cetuximab in the CApecitabine, IRinotecan, and Oxaliplatin (CAIRO) 2 study[21], this study is temporarily on hold.

CONVERSION CHEMOTHERAPY FOR INITIALLY UNRESECTABLE LIVER METASTASES

Approximately 80%-90% of patients with metastatic colorectal cancer (mCRC) referred to specialist centers have unresectable metastatic liver disease at presentation[22]. The role of chemotherapy in these patient populations is to downstage the liver lesions in an attempt to convert their disease from unresectable to resectable, while the goal of treatment for patients with little possibility of conversion to resectable disease is to prolong survival and improve quality of life.

Actually, it is more reasonable to use the term "conversion chemotherapy" than true neoadjuvant therapy[23]. The combination of 5-FU/LV with either irinotecan or oxaliplatin, or a triple cytotoxic drug combination such as fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI), with or without additional targeted agents has also been used as a preoperative strategy to achieve higher resection rates and a better clinical outcome. In a series of 44 patients with initially unresectable CLM, Alberts *et al*[24] reported their results with FOLFOX4 chemotherapy. Periodical reassessment for resectability with a high clinical RR of 60% was observed, consistent with other studies assessing the activity of FOLFOX4 as first-line therapy for colorectal cancer patients with isolated liver metastases, and 40% of these patients were able to undergo complete resection of their residual cancer. The efficacy of FOLFIRI as preoperative chemotherapy has also been demonstrated in terms of both high resection rate and favorable survival times[25-27]. In 2008, a major systematic review on irinotecan and oxaliplatin for the treatment of advanced colorectal cancer published by the United Kingdom Health Technology Assessment Agency evaluated all studies where irinotecan or oxaliplatin were combined with 5-FU to downstage patients with unresectable CLM[27]. The reported resection rates ranged from 9% to 35% for patients receiving irinotecan and 5-FU, while that for those receiving oxaliplatin and 5-FU ranged from 7% to 51%. There is no conclusive evidence that one is superior to the other as first-line therapy for the downstaging of CLM in terms of PFS and OS.

Current practice for patients whose metastases may be rendered resectable by conversion chemotherapy is to treat with the most effective regimen that offers a high RR in terms of resection rate and PFS, coupled with the recommendation that surgery should be conducted as early as possible to minimize chemical damage to the liver[6]. The effectiveness of FOLFIRI/FOLFOX draws the attention of adding a third cytotoxic drug to these regimens as initial chemotherapy in patients with CLM with good performance status for potential surgical intervention. Falcone *et al*[28] reported a phase Ⅲ randomized trial comparing FOLFOXIRI with a standard infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) regimen. Of a total of 244 patients with initially unresectable mCRC, an improved RR was achieved in the FOLFOXIRI arm (60% *vs* 34%, $P < 0.0001$). The R0 resection rate of metastases was greater in the FOLFOXIRI arm (15% *vs* 6%, $P = 0.033$, among all patients; and 36% *vs* 12%, $P = 0.017$ among patients with liver metastases only). PFS and OS were both significantly improved in the FOLFOXIRI arm (median PFS, 9.8 *vs* 6.9 mo, $P = 0.0006$;

median OS, 22.6 mo *vs* 16.7 mo, $P = 0.032$). A more recent long-term follow-up indicated that this regimen was associated with an increased RR (70.4%). The 5-year PFS for these patients was 16% and the 5-year and 8-year OS were 42% and 33%, respectively[29]. Another group demonstrated that chemotherapy with FOLFIRINOX (the same agents with FOLFOXIRI) shows a high RR (70.6%) in CLM, and further confirmed the high RR of this regimen. The rate of R0 hepatic resection in patients with initially unresectable liver metastases is attractive (26.5%)[30]. The randomized phase Ⅱ METHEP trial was conducted to compare standard double-agent chemotherapy with triple-agent intensified chemotherapy in patients with unresectable CLM. Various induction regimens including FOLFIRI, FOLFOX-4, high dose-FOLFIRI, FOLFOX-7, and FOLFIRINOX were evaluated. In the preliminary analysis after 4 cycles of treatment, the most promising regimens appeared to be FOLFIRINOX and high dose-FOLFIRI with an objective RR of 52% and 50%, respectively. Secondary resection rates of metastases were also highest in the high dose-FOLFIRI and FOLFIRINOX arms (37% and 36%, respectively). The safety profiles of FOLFIRINOX and FOLFOXIRI are generally acceptable[31].

For patients with initially unresectable CLM, disease progression during preoperative chemotherapy predicts poor prognosis, for which a change to other alternative chemotherapy regimens is usually recommended[32]. Liver resection could be reconsidered if the response evaluation shows response or stabilization after second-line chemotherapy. However, objective response rates (ORR) to second-line preoperative chemotherapy are only 4%-28%[33], and the safety of surgery in patients who received multiple lines of chemotherapy is still to be confirmed in larger series of patients. Hence, tumor progression during chemotherapy is considered a contraindication to CLM resection by most oncologists and surgery is seldom performed if patients fail first-line chemotherapy. In a recent prospective study which included the largest study population to evaluate the outcome of patients undergoing resection of CLM after a second-line chemotherapy regimen, a retrospective analysis by Brouquet *et al*[34] demonstrated that hepatectomy is safe and feasible, and associated with a modest survival benefit in these patients who present with advanced CLM who have a suboptimal response to systemic therapy, with 1-year, 3-year, and 5-year OS rates of 83%, 41%, and 22%, respectively. Although a 37% objective radiographic RR still illustrates the challenges in obtaining a tumor response with second-line chemotherapy, this rate remains acceptable compared to data reported previously[35]. This study indicated that liver resection could be considered an appropriate alternative for selected patients following second-line therapy. At the same time, due to the fact that only a few patients receiving second-line chemotherapy will benefit from resection, further investigations should be conducted to define the assessment criteria to identify potential surgical candidates in this challenging therapeutic setting.

TARGETED COMBINATION THERAPY FOR UNRESECTABLE MCRC

Abundant data are emerging from randomized trials of the added benefits conferred by the targeted agents on the prognosis of patients with unresectable mCRC, including those with CLM. Optimistic results from the randomized Cetuximab combined with iRinotecan in first line therapY for metaSTatic colorectAL cancer (CRYSTAL) trial[36] and OxaliPlatin and cetUximab in firSt-line treatment of mCRC (OPUS) trial[37] reinforce the role of cetuximab on the improvement of RRs and resection rates, combined with standard first-line chemotherapy in patients with advanced CRC. According to the published report of the CRYSTAL study, the addition of cetuximab to FOLFIRI significantly reduced the risk of progression (HR = 0.85; $P = 0.048$) and increased the ORR (HR = 1.4; $P = 0.004$), compared with FOLFIRI alone. The rate of R0 resection of secondary metastases was also slightly higher in the cetuximab-FOLFIRI arm ($P = 0.003$). Retrospective analysis suggested that the benefits of cetuximab were limited to patients with *KRAS* wild-type tumors[38]. The OPUS study which compared cetuximab plus FOLFOX to FOLFOX alone obtained similar results[37]. An update of a re-analysis of the CRYSTAL trial showed that greater benefits from the combination with cetuximab would be derived in patients with both wild-type *KRAS* and wild-type *BRAF*[39]. More patients with CLM would be rendered resectable with effective preoperative therapy, as the addition of cetuximab to chemotherapy is feasible in first-line therapy, which has been confirmed in a randomized phase Ⅱ multi-center study of cetuximab plus FOLFOX6 or cetuximab plus FOLFIRI in the preoperative setting for unresectable CLM (the CELIM study) published recently by Folprecht *et al*[40]. Partial or complete response was noted in 68% of 53 patients in the cetuximab plus FOLFOX6 arm, and 57% of 53 patients in the cetuximab plus FOLFIRI arm. In a combined analysis of both arms, 70% of patients with wild-type *KRAS* tumors achieved tumor response *versus* 42% of patients with mutated *KRAS* (OR = 3.42; $P = 0.008$). The R0 resection rates were as high as 34% in patients with wild-type *KRAS*. In retrospect, resectability rates increased from 32% at baseline to 60% after chemotherapy ($P < 0.0001$). It is concluded that cetuximab may increase the possibility of resection for patients with initially unresectable liver metastases and shows a high efficacy in the conversion treatment of CLM when combined with first-line chemotherapy. For patients with unresectable CLM refractory to conventional first-line chemotherapy, combination therapy with cetuximab could also increase resectability rates without increasing surgical mortality or liver injury[41]. A similar effective increase in RR was shown when cetuximab was added to either irinotecan- or oxaliplatin-based combinations[42-44]. However, the latest results from two randomized phase Ⅲ studies unexpectedly questioned the benefit of adding cetuximab to oxaliplatin-based combination chemotherapy[45-47]. In the MRC COIN study, 1394 patients received

oxaliplatin combination (CAPOX/FOLFOX) as standard chemotherapy with or without cetuximab. Analysis according to *KRAS* status did not result in any difference in either OS (median OS 17.9 mo *vs* 17.0 mo, $P = 0.68$) or PFS (median PFS 8.6 mo *vs* 8.6 mo, $P = 0.60$) between patients treated with CAPOX/FOLFOX and CAPOX/FOLFOX plus cetuximab, even in the *KRAS* wild-type group[45]. Only a small benefit was seen in the RR in the *KRAS* wild-type patients who received cetuximab combination therapy (59% *vs* 50%, $P = 0.02$). Further subgroup analysis reported at ASCO 2010 suggested that an interaction existed between the chemotherapy option, (CAPOX *vs* FOLFOX) and a positive effect on PFS was observed with cetuximab ($P = 0.07$), indicating a benefit from cetuximab in FOLFOX-treated patients, but not in CAPOX-treated patients. Currently, cetuximab is not recommended for combination therapies with capecitabine and oxaliplatin based on these data. Similarly, the NORDIC Ⅶ study, with 566 patients randomly assigned to receive 5-FU plus LV plus oxaliplatin (FLOX), FLOX plus cetuximab until disease progression, or FLOX intermittently plus continuous cetuximab, reported a negative result, demonstrating no added benefit when cetuximab was combined with oxaliplatin-based chemotherapy[47]. In the intent-to-treat population analysis, there were no statistically significant differences between the treatment groups in terms of RR, PFS or OS. Furthermore, the lack of benefit was also noted in both *KRAS* mutant and wild-type sub-groups, suggesting that *KRAS* status did not predict the effect of cetuximab in combination with FLOX in this study. The results from these two studies do not support the use of cetuximab in first-line therapy when given together with oxaliplatin-based regimens. Thus, caution should be taken when making decisions on combined chemotherapy regimens as the role of anti-EGFR agents in the first-line treatment of mCRC needs to be explored further.

In addition, cetuximab combined with triple cytotoxic drug therapy is also being evaluated, for potential extra efficacy on RR and clinical outcome[48,49]. Definitive results from the preoperative chemotherapy for hepatic resection (POCHER) study revealed an RR of 79% and a complete resection rate of 63% achieved by FOLFOXIRI plus cetuximab[48]. Preliminary results of another phase Ⅱ trial evaluating cetuximab in combination with FOLFIRINOX demonstrated an ORR as high as 82% and predicted the feasibility of this new therapeutic combination in first-line mCRC patients[49].

KRAS had been broadly accepted as a predictive factor of anti-EGFR antibody therapies prior to the negative results of the NORDIC Ⅶ study, and identification of additional predictors such as *BRAF* has attracted significant interest. A recent meta-analysis based on the CRYSTAL and OPUS trials reported the updated clinical efficacy of cetuximab combination therapy according to *KRAS* and *BRAF* mutation status[50]. This analysis confirmed that in *KRAS* wild-type patients, the addition of cetuximab in first-line treatment achieves a statistically significant improvement in RR, PFS, and OS compared with chemotherapy alone. However, it also concluded that *BRAF* mutation status does not appear to be a strong predictive biomarker for the addition of cetuximab. *BRAF* is more likely to be a prognostic factor as the clinical outcome in *BRAF*-mutant patients is worse than those with *BRAF* wild-type tumors in terms of RR, PFS and OS. Thus, *BRAF* testing is probably not essential when deciding whether cetuximab should be used. Larger clinical trials to further investigate the field of predictive molecular biomarkers are required since the present data are inconsistent.

The role of bevacizumab added to chemotherapy in the perioperative setting for initially unresectable metastases was evaluated in two large multi-center prospective trials (First BEAT and NO16966)[51]. The First BEAT trial reported a 6% R0 hepatic resection in an unselected population and 12.1% among patients with isolated liver metastases only. Resection rates were highest in patients who received oxaliplatin-based combination chemotherapy ($P = 0.002$). In NO16966[52], the addition of bevacizumab to XELOX/FOLFOX significantly improved PFS in the first-line therapy (9.4 mo *vs* 8.0 mo, $P = 0.0023$), but there were no statistically significant differences between resection rates or OS in patients treated with bevacizumab plus XELOX/FOLFOX *vs* placebo (6.3% *vs* 4.9%, $P = 0.24$). Bevacizumab improved RR when added to FOLFIRI regimen but did not improve RRs and resection rates when added to XELOX or FOLFOX. Recent data from a small phase Ⅱ trial by the GONO group revealed that FOLFOXIRI plus bevacizumab yielded an ORR of 76% and a disease control rate of 100%, with a secondary resection of metastases in 17% of patients[53]. It seems that the addition of bevacizumab to FOLFOXIRI regimen is effective with manageable toxicities, however, negative reports on its efficacy in heavily pretreated patients with advanced disease and its role as adjuvant therapy for stage Ⅲ colon cancer in the NSABPC-08 study remind us to be cautious of the optimal stage to start administration and to determine the best treatment sequence[54,55].

Results from the PACCE study[20] and CAIRO2 study[21] failed to demonstrate a biological synergistic effect in antibodies both against the EGFR (cetuximab or panitumumab) and VEGF (bevacizumab). Thus, specific combinations of targeted drugs are not recommended as first-line therapy for patients with mCRC, including CLM. The ongoing CALGB/SWOG 80404 trial which compared the addition of cetuximab, or bevacizumab or both to standard FOLFIRI/FOLFOX should help to define the preferred targeted partner primarily in terms of OS. The RR, PFS and the resection rate will be secondary end points[56].

LOCOREGIONAL CHEMOTHERAPY

Patients with multifocal CLM who are unfit for surgery or have tumor distribution technically unresectable with clear margins, are potential candidates for regional liver chemotherapy. Hepatic arterial infusion (HAI) with chemothera-

peutic agents can provide relatively high concentrations of drugs to micro- or macro-metastases remaining in the liver with less toxicity to extrahepatic organs. The most commonly used agent for HAI is Floxuridine (FUDR) which is an analogue of 5-FU, and has the advantage of having a first-pass extraction rate of over 94% within the liver[57]. For those whose liver metastases were initially unresectable, the use of HAI as pre-operative conversion therapy to downstage the disease for resection was recommended in some early studies, due to the efficacy results obtained[58-60]. A recent Cochrane meta-analysis of ten randomized trials which compared HAI with fluoropyrimidine chemotherapy to systemic chemotherapy or best supportive care in patients with initially unresectable liver metastases suggested that administration of fluoropyrimidines through HAI yielded higher tumor RRs as compared to the systematic chemotherapy regimens (42.9% *vs* 18.4%, $P < 0.0001$). However, this anticancer activity does not translate into a significant survival advantage for patients treated with HAI as compared to those given systemic chemotherapy (15.9 mo *vs* 12.4 mo)[61]. Only one out of ten studies indicated that HAI with 5-FU was superior to systemic bolus 5-FU/LV in terms of RR and survival[62]. Altogether, current data do not support the clinical or investigational use of fluoropyrimidine-based HAI alone in patients with initially unresectable liver metastases. The advantages of systemic oxaliplatin or irinotecan-based chemotherapy over the 5-FU/LV regimen also guided the use of these agents in HAI chemotherapy. Encouraging results were obtained in patients with initially unresectable metastases, with RRs as high as 55%-70% and resection rates of approximately 16%-18% in unresectable liver metastases[63,64].

HAI as post-operative chemotherapy was also investigated in some clinical trials for feasibility in CLM. A Cochrane meta-analysis performed on seven randomized trials with a total of 592 patients did not show improvement on OS in the HAI group even though fewer recurrences were noted in the remaining liver[65]. As early as 1999, Kemeny *et al*[66] reported the results from a single-institution study in which 156 patients were randomized to post-operative HAI with FUDR plus systemic 5-FU ± LV *vs* systemic therapy alone. An increase in two-year survival rate for the combination therapy group was observed (90% *vs* 60%, $P < 0.001$) as compared with the group receiving monotherapy. The liver relapse-free survival also significantly increased in the combination therapy group. Furthermore, an updated analysis with a median follow-up of 10.3 years reports a significantly greater PFS rate (31.3 mo *vs* 17.2 mo, $P = 0.02$) and a trend toward improved OS (68.8 mo *vs* 58.8 mo, $P = 0.10$) in the combined therapy group compared to the monotherapy group[67]. Other similar randomized studies also suggested an improved PFS of the liver in the HAI combination group compared to the control group, but none of these studies showed any advantage in OS and long-term DFS[68,69].

Negative outcomes in terms of OS and significant hepatobiliary toxicity related to HAI as well as the expertise required limit the implementation of this technique. Given the availability of an increasing number of active systemic chemotherapy regimens, especially the biologic agents, the value of HAI chemotherapy is less clear.

CONCLUSION

Surgical resection undoubtedly remains the gold standard for the treatment of resectable CLM. A well coordinated multidisciplinary approach is also necessary to achieve optimal outcomes for patients with CLM. The modality of perioperative chemotherapy over surgery alone has resulted in more patients with initially unresectable metastases receiving a complete resection and enjoying a prolonged survival after surgery. Emerging data has revealed that preoperative chemotherapy, as well as postoperative chemotherapy could be advantageous compared to surgery alone in terms of DFS for patients with resectable CLM. Newly emerging biologic targeted agents when added to the standard chemotherapy regimen have contributed to increased tumor RR, and to a larger extent, higher secondary resection rates. Insight into the molecular markers to predict the outcome of targeted therapy may define subgroups of patients within the same stage.

At present, there is insufficient evidence to demonstrate the efficacy of regional perioperative chemotherapy. Multi-center randomized prospective trials are needed to provide evidence of a survival advantage of regional perioperative chemotherapy with acceptable adverse effects.

Even though the intent of preoperative therapy followed by resection is probably curative, cure is rarely achieved, as the majority of patients who undergo hepatic resection will experience recurrence. More potent agents and strategies have to be developed to provide longer survival time and eventually cure this disease.

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