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Chemotherapy and Regional Therapy of Hepatic Colorectal Metastases: Expert Consensus Statement

David L. Bartlett, MD,[1] Jordan Berlin, MD,[2] Gregory Y. Lauwers, MD,[3] Wells A. Messersmith, MD,[4] Nicholas J. Petrelli, MD,[5] and Alan P. Venook, MD[6]

[1]Division of Surgical Oncology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[2]Division of Internal Medicine and Medical Oncology, Vanderbilt Ingram Cancer Center Nashville, Tennessee, USA
[3]Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA
[4]Gastrointestinal Oncology Program, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland, USA
[5]Department of Surgery, Helen F. Graham Cancer Center, 4701 Ogleton Stanton Road, Suite 1233, Newark, Delaware 19713, USA
[6]Department of Clinical Medicine, University of California-San Francisco, 600 Divisadero, P.O. Box 1770, San Francisco, California, USA

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SYSTEMIC CHEMOTHERAPY FOR UNRESECTABLE PATIENTS

The treatment of metastatic colorectal cancer has evolved significantly over recent years. Where once only 5-fluorouracil (5-FU) was available for treatment, there are now five active agents available for the treatment of advanced disease. Two new chemotherapy agents are now available: oxaliplatin and irinotecan. When added to either bolus or infusional 5-FU, irinotecan significantly increased the survival of colorectal cancer patients compared to those given 5-FU alone.[1,2] When oxaliplatin plus infusional 5-FU (FOLFOX) was compared to irinotecan plus bolus 5-FU (IFL), both the response rate and survival were improved in the oxaliplatin-containing arm.[3] However, two randomized trials have shown that when 5-FU is administered by the same schedule in each arm, survival is similar in both the irinotecan- and oxaliplatin-containing arms.[4,5] Therefore, treatment decisions for first-line therapy can be made based on the toxicity profile of individual drugs or on personal preference but not because of significant differences in efficacy. Both FOLFOX and irinotecan have demonstrated efficacy as second-line therapy.[6,7]

More recently, agents that target angiogenesis (VEGF inhibitors) and the epidermal growth factor receptor (EGFR) have been approved for use in colorectal cancer.

When added to IFL therapy as first-line therapy, bevacizumab, an anti-VEGF antibody, increases the response rate, progression-free survival, and overall survival of colorectal cancer patients compared to IFL alone.[8] As second-line therapy, the Eastern Cooperative Oncology Group study (ECOG 3200) demonstrated that bevacizumab improves the response rate, progression-free survival, and overall survival compared to FOLFOX alone.[9] Only bevacizumab-naïve patients were tested in ECOG 3200, so there are no data available to suggest that continuing bevacizumab from first- to second-line therapy is of benefit. Another inhibitor of the VEGF

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Address correspondence and reprint requests to: Nicholas J. Petrelli, MD; E-mail: npetrelli@christianacare.org
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pathway, PTK 787, has not shown the same beneficial results as bevacizumab. In first-line therapy of colorectal cancer, PTK 787 failed to meet its primary progression-free survival endpoint.[10] It is unclear why this method of targeting the VEGF pathway was ineffective while the antibody was effective. However, the schedule by which the PTK 787 was administered may have played some role. A second-line trial comparing FOLFOX + PTK 787 versus FOLFOX alone also failed to show any benefit of including PTK 787 in the therapy, but these data have only been presented as a press release.

The second signaling pathway being targeted in colorectal cancer is that of the EGFR. Cetuximab, a chimerized antibody to the EGFR, has been tested after irinotecan failure, both with and without a continuation of the irinotecan therapy. Response rates are doubled when cetuximab is given together with irinotecan, and progression-free survival is prolonged.[11] However, because cetuximab has never been tested against a non-cetuximab-containing control arm, it is unknown if this agent benefits colorectal cancer patients in terms of survival. The effects of a human antibody to the EGFR, panitumumab, look remarkably similar to those of cetuximab alone.[12] Additionally, the cetuximab data have been remarkably consistent from trial to trial, suggesting that the antitumor effects of monoclonal antibodies to EGFR are very reproducible.[13] Despite a lack of data on survival, it is expected that the demonstrated anticancer activity of these agents will result in some benefit to colorectal cancer patients. Both panitumumab and cetuximab are currently being evaluated as first-line treatment in combination with chemotherapy. To date, small-molecule tyrosine kinase inhibitors of the EGFR pathway have not demonstrated efficacy.[14]

When chemotherapy agents are combined, such as in the FOLFOX or FOLFIRI regimens, the effects are clearly better than may be predicted by the sum of the parts.[2,3,7,14] In a similar fashion, an early trial evaluating cetuximab + bevacizumab, with or without irinotecan, in patients with metastatic colorectal cancer obtained high-response rates and progression-free survival times for both arms.[15] Therefore, current first-line trials are combining bevacizumab with the EGFR antibodies to take advantage of this potential synergy. In parallel, the iBET trial compared second-line irinotecan + cetuximab versus irinotecan + cetuximab + bevacizumab in patients who had previously been treated with FOLFOX + bevacizumab.

In summary, five active agents are available in 2006 for the treatment of metastatic colorectal cancer. While developing future agents in new clinical trials, it is incumbent on investigators to learn how best to use the current agents to maximize survival for all patients with unresectable metastatic disease.

Consensus Statement:

1. Standard of care is either infusional 5-FU, leucovorin and irinotecan (most commonly FOLFIRI) in combination with bevacizumab, or infusional 5-FU, leucovorin, and oxaliplatin (most commonly FOLFOX) with bevacizumab.
2. If FOLFOX + bevacizumab are used as first-line therapy, irinotecan or FOLFIRI should be the second-line regimen. Upon progression, cetuximab should be added. While it may be reasonable to add cetuximab immediately in the second-line regimen, rather than waiting for progression on irinotecan, current Food and Drug Administration (FDA) approval would suggest the first plan.
3. If FOLFIRI + bevacizumab is administered first, then second-line therapy can be FOLFOX or irinotecan + cetuximab.
4. Testing of the tumor for EGFR expression has been suggested prior to cetuximab use, but this is of no predictive value.
5. Enrollment in clinical trials, particularly the cooperative group trials, remains crucial to determining the optimal use of available agents.

ADJUVANT THERAPY FOR RESECTED HEPATIC COLORECTAL METASTASES

Principles of Adjuvant Therapy in Primary Colorectal Cancer

Adjuvant treatment with 5-FU-based chemotherapy has been accepted as a standard approach following resection of node-positive primary colorectal cancers. This is based on several trials that have shown a substantial survival benefit with adjuvant therapy.[16–20] The absolute benefit for adjuvant treatment appears to increase with the risk of relapse; for example, the benefit for node-positive (stage III) patients is quite clear and has been demonstrated in trials with 500–3000 patients. The absolute benefit for node-negative (stage II) patients, on the other hand, appears to be smaller, and the role of adjuvant treatment these patients is controversial.[21–23] It has

been estimated that a trial with over 5000 stage II patients would be required to definitively demonstrate a survival benefit.[24] In contrast, given the comparatively high risk of recurrence following the resection of hepatic colorectal metastases, one would not expect the required number of subjects for a clinical trial to be prohibitive. Despite this, there are only a few clinical trials addressing adjuvant treatment following the resection of hepatic colorectal metastases.

There are several options available for the adjuvant chemotherapy of stage III colon cancer. Based on the results of the MOSAIC trial,[23] many consider the gold standard to be the combination of infusional 5-FU, leucovorin (LV, or folinic acid), and oxaliplatin in the FOLFOX regimen. This pivotal study randomized patients to 6 months of infusional 5-FU/LV with or without oxaliplatin and showed an improvement in the 3-year disease-free survival of the patients in the oxaliplatin arm, which has been widely accepted as a reliable surrogate endpoint for overall survival.[25] Interestingly, in NSABP C-07, a different schedule of bolus 5-FU/LV with oxaliplatin (FLOX) has also shown an improved disease-free survival.[26] 5-FU/LV alone can also be successfully administered without oxaliplatin in a variety of doses and schedules. More recently, an oral prodrug of 5-FU, capecitabine, has been shown to be equally effective and better tolerated than monthly bolus 5-FU in stage III patients.[27] To the surprise of many, given its activity in the advanced disease setting, irinotecan has not shown the same benefit when added to 5-FU/LV in large trials and is not recommended.[28–30] This finding has called into question whether the responsiveness of tumors in metastatic disease (where both irinotecan and oxaliplatin appear to be equally active) is the same as that in localized disease (where oxaliplatin appears to be more effective). Thus, extrapolation from the advanced to the adjuvant setting has limits, as yet not clearly understood.

Most currently enrolling adjuvant trials are evaluating the role of the "biologic" agents bevacizumab (antibody against VEGF) and cetuximab (antibody against EGFR) in the adjuvant setting. The results from these studies are not expected for several years.

Adjuvant Therapy for Resected Liver Metastases

Given the comparatively high risk of relapse following the resection of metastatic disease to the liver as compared to primary colorectal cancers, it comes as no surprise that most medical oncologists recommend some type of adjuvant chemotherapy following partial hepatectomies. The lack of data supporting such practice, however, is striking. The optimal drug combination, schedule, timing, and duration remain unknowns. There have been few trials with substantial numbers of subjects prospectively randomizing to chemotherapy versus observation, or to different chemotherapy regimens, for resected hepatic colorectal metastases.[31–33] Much of the existing data regarding adjuvant treatment deal with hepatic arterial infusion versus systemic chemotherapy or versus observation.[34,35] Indeed, there is a paucity of even small feasibility or safety-oriented phase II studies for adjuvant chemotherapy following liver resection.

There are two recent studies comparing chemotherapy to observation in the adjuvant setting following hepatic resection. The final results from both trials are pending. In the FFCD 9002 trial, 167 patients were randomized to either monthly bolus 5-FU/LV or observation.[33] There was an improvement in 5-year disease-free survival in the former group, from 24% in the surgery alone group to 33% in the 5-FU/LV group. Grade 3/4 toxicities were noted in 25% of the patients. Of note, it took 10 years to fully enroll an adequate number of patients to this trial, which speaks to the challenge of doing such trials. In the EORTC 40983 (EPOC) trial, the issue of perioperative FOLFOX chemotherapy was addressed.[32] In total, 354 subjects with potentially resectable hepatic colorectal metastases were randomized to either surgery alone (without chemotherapy) or to 3 months of FOLFOX followed first by surgery and then by another 3 months of FOLFOX (a total of 6 months). Efficacy results are pending, but from a toxicity standpoint the chemotherapy appeared to be well-tolerated and did not interfere with successful surgery. The most common grade 3/4 adverse event was neutropenia (14%), followed by diarrhea (6%). There was no difference in perioperative mortality, although post-operative complications were more frequent in the chemotherapy-treated group (21 vs. 10%).

There have been several small phase II studies examining the feasibility of adjuvant chemotherapy following liver resection. One recently published study showed that six 21-day cycles of irinotecan following hepatic resection is feasible, with an estimated relapse-free survival of 45.2 months; however, only 29 patients were treated and an across-the-board dose-reduction was required.[36] Intravenous irinotecan has also been safely combined with the hepatic arterial infusion drug fluorodeoxyuridine (FUDR) following liver resection.[34]

Radioimmunotherapy has also been employed as an adjuvant treatment following resection.[37] Larger studies of all of these adjuvant treatments will be necessary.

Adjuvant chemotherapy following hepatic resection presents a dilemma for which there is no single standard approach. On the one hand, it can be argued that aside from centers with specialization for hepatic infusion pumps, no adjuvant therapy should be given since efficacy is unproven. On the other hand, a reasonable point can be made that since adjuvant therapy following resection of primary colorectal cancers has a proven role and chemotherapy for advanced disease has improved outcomes, all patients should be given some type of systemic therapy following hepatic resection. Similar arguments can be made regarding the inclusion of "biologic" therapies such as cetuximab and bevacizumab, which have a definite role for patients with advanced disease but are, as yet, of unproven benefit in the adjuvant setting following resection of either primary cancers or hepatic metastases. The results of the N0147 intergroup adjuvant trial, randomizing to FOLFOX with or without cetuximab, and the NSABP C-08 trial, randomizing to FOLFOX with or without bevacizumab, following the resection of primary tumors should help clarify this issue. Both trials are currently enrolling.

Consensus Statement:

1. Even though there are no published level I or II data supporting the use of chemotherapy for initially resectable hepatic colorectal metastases, the rationale for its use by extrapolation from response rates seen in treating metastatic colorectal cancer probably justifies it being offered to selected patients. This rational is further supported by the fact that most patients with hepatic colorectal metastases also have concomitant extrahepatic disease that would theoretically benefit from systemic chemotherapy.
2. Both adjuvant and advanced-disease regimens can reasonably be offered, depending on the patient's previous treatment and response, performance status, organ function, and other factors.
3. The optimal duration of adjuvant systemic chemotherapy following liver resection is unknown, but most oncologists utilize 4–6 months of systemic chemotherapy.
4. If bevacizumab is employed as adjuvant therapy, the recommendation is to discontinue this drug approximately 8 weeks prior to surgery and/or to wait 8 weeks following surgery due to possible issues with wound-healing and other complications.[38]
5. Enrollment in clinical trials is strongly encouraged to better define the efficacy and toxicity of adjuvant therapy following hepatic resection.

INTRA-ARTERIAL APPROACHES (INFUSION, CHEMOEMBOLIZATION, RADIOEMBOLIZATION, ISOLATED PERFUSION)

Techniques for regional hepatic therapy for metastatic colon cancer to the liver include hepatic arterial infusion chemotherapy, chemoembolization, infusion radiotherapy with yttrium-90 labeled particles, and isolated hepatic perfusion. While these approaches have been available for a long time, their role in the management of metastatic colon cancer continues to evolve. Recent improvements in systemic chemotherapy for metastatic colon cancer should force oncologists to re-evaluate the role of regional hepatic therapy. It is essential to evaluate the indication and timing for these approaches.

Hepatic arterial infusion (HAI) chemotherapy has been the best studied of the approaches mentioned.[39] The delivery of chemotherapy to the liver via the hepatic artery has the advantage of higher chemotherapy exposure to the tumor over a longer period of time. FUDR has been the most commonly studied drug for this purpose. It has a high first-pass metabolism/clearance through the liver that minimizes the chances for systemic toxicity. This advantage leads to high response rates, where 35–83% of patients will have an objective radiologic response.[40] In several randomized trials of patients with unresectable disease, this treatment has been compared to systemic therapy or to no therapy at all for colon cancer. A meta-analysis of multiple randomized trials demonstrated an improvement in response rate from 14–41% and a 27% relative survival advantage ($P = 0.0009$),[41] while two subsequent randomized trials did not demonstrate improved survival compared to control arms.[34,42] This treatment approach is limited by hepatic toxicity and technical problems related to catheters, arterial ports, and implantable pumps. In a recent randomized trial from the Medical Research Council (MRC) and European Organization for Research and Treatment of Cancer (EORTC) colorectal cancer study groups, only 63% of

patients intended to receive HAI ever started therapy, and the median number of cycles was two.[42] Newer combination systemic chemotherapy for metastatic colorectal cancer now rivals response rates for HAI therapy and is currently favored over the more labor-intensive HAI therapy. Future studies need to examine whether the addition of HAI therapy to standard systemic chemotherapy demonstrates an advantage in terms of survival compared to systemic therapy alone. Kemeny et al. reported a 90% response rate and 36-month median survival when HAI therapy was combined with systemic oxaliplatin and irinotecan. HAI therapy should be used as an adjunct to systemic chemotherapy—and not as a replacement for systemic chemotherapy.[43]

HAI chemotherapy has also been used in adjuvant setting after liver resection. In a multicenter randomized trial comparing post-operative HAI (FUDR) plus systemic infusion of 5-FU versus no treatment the 4-year overall survival rate was no different between groups despite a better 4-year disease-free survival in the chemotherapy arm (46 vs. 25%)[35] In another study, Kemeny et al.[34] randomly assigned 156 patients who had undergone resection of hepatic colorectal metastases to HAI (FUDR and dexamethasone) plus systemic chemotherapy (5-FU with or without LV) or chemotherapy alone (5-FU +/− LV). After a median follow-up of 62.7 months the median overall survival did not differ between the two groups. In a subsequent analysis of the same patient cohort, significantly better overall progression-free survival was noted in the combined-therapy group (31.3 vs. 17.2 months), but no significant improvement in 5- and 10-year overall survival was obtained.[44] It is important to note that this study did not use new chemotherapy agents (oxaliplatin or irinotecan) for systemic treatment. With the availability of newer drugs for systemic therapy, the role of HAI as adjuvant treatment remains to be defined. The results of ongoing studies will help to clarify whether or not HAI is beneficial as post-operative adjuvant therapy. For example, the National Surgical Adjuvant Breast and Bowel Project (NSABP) is presently accruing patients to Protocol CO9, which randomizes patients with resectable/ablatable metastases (≤6 metastases) to either systemic capecitabine + oxaliplatin or the same in combination with IA-FUDR following surgery.

Transarterial chemoembolization or embolization without chemotherapy has developed as a successful treatment for hepatocellular cancer and has been applied to colorectal cancer metastases. This treatment is applied via a percutaneous catheter advanced into the hepatic artery and is associated with less technical complications than HAI therapy. The embolization treatment leads to the acute ischemic necrosis of tumors by blocking arterial flow to the tumors. This results in the death of most, but not all, cells within a tumor. Tumors with slowly dividing cells can be treated successfully with multiple embolizations over many months. Faster growing tumors will recur quickly between treatments and will not respond well overall to this approach. Nineteen trials have evaluated chemoembolization for colorectal cancer metastases in 324 patients.[45] Response rates vary from 25 to 100% depending on the criteria used for measuring response, and a median survival of between 7 and 23 months has been reported. These results have not been adequately compared to other forms of regional therapy for the liver and, therefore, chemoembolization should not be considered to be standard therapy for colorectal metastases.

An alternative approach to infusional chemotherapy is infusional radiotherapy using yttrium-90 microspheres. These microspheres are infused into the common hepatic artery via a percutaneously or surgically placed catheter, and they preferentially localize to the tumor vasculature and emit therapeutic radiation. Two commercially available ^{90}Y-microspheres exist for this selective internal radiation therapy (SIRT): SIR-Spheres (made of resin), and Thera-Spheres (made of glass). SIR-Spheres are approved by the FDA for treating unresectable metastatic liver tumors from primary colorectal cancer and are commonly used in combination with infusional FUDR. A phase III trial in 71 patients demonstrated an improved response rate and time to progression (9.7 vs. 15.9 months, $P = 0.001$) comparing intra-arterial FUDR alone to FUDR plus SIR-Spheres.[46] A randomized phase II study demonstrated an improved survival from 12.8 to 29.4 months with SIR-Spheres plus systemic 5-FU/leucovorin compared to systemic therapy alone.[47] Toxicity with this approach is secondary to the escape of radioactive microspheres from the liver leading to damage of other organs, such as the stomach or duodenum, lung, and bone marrow. In general, however, this therapy is very well tolerated.

Isolated hepatic perfusion (IHP) is a surgical technique where the liver vasculature is completely isolated from the rest of the body and perfused with chemotherapy.[48] The dose of chemotherapy is limited only by hepatotoxicity as no drug can leak out of the perfusion circuit during the perfusion. Careful phase I and phase II trials have been performed defining the maximum tolerated dose of IHP with melphalan. In

19 patients treated with IHP with melphalan followed by HAI with FUDR, the objective radiographic response rate was 74% and the median survival was 27 months.[49] Rothbarth et al. reported a response rate of 59% and median survival of 29 months in patients treated with IHP with melphalan alone.[50] Newer techniques have simplified the IHP technique, and a phase I trial of IHP with oxaliplatin is currently accruing patients.

Consensus Statement:

1. Although numerous successful approaches exist for the regional therapy of hepatic metastases from colorectal cancer, these approaches should not be considered outside of investigational protocols.
2. Given the effectiveness of systemic chemotherapy, regional chemotherapy should be used in conjunction with systemic chemotherapy.
3. Too little data exist to determine an overall advantage of one form of regional therapy over another; however, chemoembolization is the least appealing option and can no longer be recommended.
4. Clinical trials comparing regional therapy plus systemic chemotherapy to systemic chemotherapy alone should be performed to define the role for each approach in the management of patients with hepatic metastases from colorectal cancer.

STEATOSIS AND CHEMOTHERAPY-ASSOCIATED LIVER INJURY

5-FU based chemotherapy protocols, as well as new regimens, have been associated with increased resectability rates of hepatic colorectal metastases and have brought renewed hope for cure. Not surprisingly, clinical, biologic, and microscopic hepatotoxic manifestations of these drugs have also been recognized. The histologic complexity of the liver accounts for the diversity of damage to hepatocytes, endothelial cells, cholangiocytes, and stellate cells. In this section we review the morphologic aspects highlighted in recent studies.

Chemotherapy-Associated Steatosis and Steatohepatitis

Non-alcoholic fatty liver disease (NAFLD), which encompasses steatosis and steatohepatitis, is reported in up to 3% of the general population and up to two-thirds of individuals with morbid obesity. The exact mechanisms leading to NAFLD remain obscure; however, obesity and insulin resistance are common risk factors.

Several series have emphasized a higher risk of post-operative morbidity and mortality in patients with marked hepatic steatosis that can impair liver regeneration.[51,52] Over the years, an association between cytotoxic chemotherapy and steatosis has been reported. The development of steatosis has been associated with 5-FU and levamisole which, as mentioned above, are used in adjuvant therapy for stage III colorectal cancers.[53] In another series, 47% of patients receiving 5-FU and folinic acid for advanced colorectal cancers had radiologic evidence of fatty changes.[54] Reversible steatosis has also been reported in 30% of patients treated with a combination of α-interferon and 5-FU.[55] More recently, the association between preoperative chemotherapy and the development of steatosis has been underscored.[52] In a retrospective series of 248 patients receiving preoperative chemotherapy, irinotecan was associated with steatohepatitis in 20% of the patients, compared to 4.4% in patients who received no chemotherapy ($P < .0001$).[56] Furthermore, although mild in most patients, severe steatohepatitis has been found to be associated with increased post-operative risk of mortality within 3 months of surgery, particularly in patients where there have been extensive resection attempts.[56] However, the association between chemotherapy and steatosis/steatohepatitis has not been universally accepted, and there is continuing debate over the relative importance of the number of chemotherapy cycles, their delivery (chronomodulation), and a patients' individual traits, such as elevated body mass index (BMI).[56–58]

Hepatic Sinusoidal Obstruction Associated with Oxaliplatin-based Chemotherapy

Oxaliplatin is a proven, generally safe, and effective, platinum-based chemotherapy that has recently been shown to induce sinusoidal distention. The sinusoidal dilatation can vary from mild to marked, with extravasation of erythrocytes in Disse's space. Fibrosis of the perisinusoidal spaces and centrolobular veins has also been identified.[59] It is hypothesized that toxic injury to the sinusoidal endothelial cells leads to activation of hepatic stellate cells and the deposition of matrix.[59] The incidence of oxaliplatin toxicity has not been widely reported. In two

independent studies published in 2004 and 2006, Rubbia-Brandt and Karoui reported about a 50% incidence of sinusoidal dilatation, peliosis, and atrophy of hepatocytes in patients receiving preoperative oxaliplatin-based chemotherapy protocols.[58,59]

Whether oxaliplatin is solely responsible for this alteration or whether the toxicity is linked to the combination with other chemotherapeutic agents (e.g., 5-FU) in a synergistic manner has not been fully investigated. However, recent data confirm the privileged association with oxaliplatin in comparison with other therapeutic regimens.[56] Less frequently reported changes developing after oxaliplatin-based therapy are hemorrhagic centrolobular necrosis and nodular regenerative hyperplasia.[59]

Fibrosis may persist despite the discontinuation of chemotherapy and the detection of cirrhosis.[59] However, with the exception of one patient who developed portal hypertension and ascites and eventually died, there are no reports in the literature of an association between oxaliplatin toxicity and increased post-operative mortality.[56,60] Others, however, have observed increased intra-operative transfusion rates, particularly with prolonged preoperative chemotherapy protocols (>12 courses).[61]

Hepatotoxicity of 5-FU

Nodular regenerative hyperplasia (NRH), a diffuse parenchymal reactive process, has been reported in 15% of patients receiving preoperative 5-FU-based chemotherapy for metastatic colorectal metastases.[62] NRH is characterized by an ill-defined parenchymal nodularity formed by alternating areas of expanding nodules of hyperplastic hepatocytes with sinusoidal congestion and compression of peripheral parenchyma and central veins. The pathogenesis of NRH, which appears to develop within weeks of the completion of chemotherapy, is unknown, although it is believed to be related to a modification of the intrahepatic blood flow. However, no morphologic vascular alteration has been reported in that setting.[62] It is likely that NRH regresses when the treatment is discontinued. Of note, NRH has also been reported in the setting of oxaliplatin therapy.[59]

Hepatotoxicity of FUDR

HAI is one approach to achieve high hepatic levels of cytotoxic agents with concurrent limited systemic toxicity. FUDR, the drug of choice, with 90% extracted at the first pass, has a toxicity that is dependent on both the duration of the treatment and the dose.[63] Several patterns of injury can be seen. In addition to "chemical hepatitis" noted in about 40% of patients, ductular damage of the intra- and extrahepatic bile ducts has been reported in up to 26% of patients.[63] The classical alteration includes bile duct sclerosis, which principally involves the extrahepatic biliary tract but often spares the distal common bile duct, thereby providing an injury pattern reminiscent of primary sclerosing cholangitis. Morphologically, the lining epithelium is either eroded or atrophic, and the duct wall is markedly fibrosed.[64] Acalculous cholecystitis also develops in about one-third of the patients, and prophylactic cholecystectomy is recommended.[65] Hepatic parenchymal changes may include mild to moderate triaditis, portal fibrosis with bridging, ductular proliferation, cholestasis, and central vein fibrosis.[66]The injury results from an obliterative vasculopathy involving both the artery and veins, with secondary ischemic damage.[64]

Portal Vein Thrombosis Associated with Bevacizumab

Partial portal vein thrombosis following treatment by bevacizumab, an anti-vascular endothelial growth factor A (VEGF-A) murine monoclonal antibody, has recently been observed.[67] Although not previously reported in the portal circulation, a high incidence of arterial thrombotic events has been noted.[68] The exact mechanism leading to hypercoagulability in association with bevacizumab has not been completely elucidated. However, it is believed that the anti-VEGF activity ultimately leads to the apoptosis of endothelial cells, which in turn allows the exposure of subendothelial cells and triggers a coagulation cascade.[69]

Consensus Statement:

1. Most chemotherapeutic agents used for the management of hepatic colorectal metastases are associated with various histological patterns of liver injury, but the incidence and pathogenesis are not well established.
2. In the spectrum of complications, steatohepatitis is a matter of rising concern, most particularly when irinotecan is employed.
3. The relative contributions that BMI, diabetes, and dosing factors, such as the number of cycles and chronochemotherapy, have on chemotherapy-induced liver injury remains to be fully determined.

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