Chemotherapy and Other Systemic Therapies for Hepatocellular Carcinoma and Liver Metastases

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ABSTRACT

For hepatocellular carcinoma (HCC) that has advanced to the point that it is no longer amenable to local therapies, systemic therapy can be considered in select patients who have a good performance status. No systemic therapy has been clearly shown to improve overall survival compared with supportive care alone, although cancer-related symptoms can sometimes be palliated with therapy and some objective responses are seen. Systemic therapies for HCC include chemotherapy, both intravenous and infused via the hepatic artery, as well as hormonal therapy, immunotherapy, and targeted biologic agents. Colorectal, pancreatic, breast, and lung cancer are some of the most common tumors that metastasize to the liver. Response rates and effect on overall survival as a result of systemic therapy for liver metastases vary widely depending on primary tumor site. Targeted biologic agents are being integrated into standard treatment regimens for all of these cancer types, with variable effects on survival and other outcomes for all affected patients including those with liver metastases.

KEYWORDS: Hepatocellular carcinoma, chemotherapy, systemic therapy, liver metastases

Objectives: On completion of this article, the reader should understand (1) the indications for treating hepatocellular carcinoma and liver metastases with systemic therapy, and (2) the most commonly used systemic therapies, their mechanisms of action, and their effects on clinical outcomes.

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It is often necessary or preferable to use chemotherapy or other systemic therapy to treat malignancies affecting the liver, either for primary liver cancer or cancer metastatic to the liver. Chemotherapeutic and other systemic approaches to hepatocellular carcinoma (HCC) as well as some tumors that commonly involve the liver (colorectal, breast, lung, and pancreatic cancer) will be discussed here.

HEPATOCELLULAR CARCINOMA

HCC is one of the most common malignancies worldwide and is a growing problem in the United States, due in large part to the increasing incidence of hepatitis C infection in this country. For patients who present with HCC that has not metastasized beyond the liver, local approaches are generally preferred. In those patients who present with extrahepatic disease, as well as

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Table 1 Performance Status Assessment Using Zubrod (ECOG) and Karnofsky Scales

Zubrod (ECOG)	Karnofsky (%)	Definition
0	100	Asymptomatic
1	80–90	Symptomatic, fully ambulatory, able to care for self
2	60–70	Symptomatic, spending less than, half of day in bed, may require occasional assistance
3	40–50	Moderate to severe disability, requires frequent assistance, spends more than half of day in bed
4	20–30	Severely disabled, bedridden

ECOG, Eastern Cooperative Oncology Group.

for those with liver-confined disease not amenable to resection or other local therapies, systemic therapy can be considered. Systemic and intra-arterial chemotherapy, hormonal therapy, immunotherapy, and novel targeted agents will be discussed here. Many agents have been studied in this disease, often in relatively small clinical studies. This review will attempt to focus on the most relevant agents and studies.

Common sites of metastasis for HCC include intra-abdominal lymph nodes, lungs, and bone. For many patients with HCC, abdominal pain is the predominant symptom; bone pain is frequently seen in those patients with bone metastases. Patients with lung metastases can often suffer from dyspnea, cough, and occasionally hemoptysis. Anorexia and weight loss are also common. All of these symptoms can potentially be ameliorated by chemotherapy in responding patients, in conjunction with other palliative therapies such as narcotic analgesics.

CHEMOTHERAPY

Chemotherapy is often offered to patients with advanced HCC who have an adequate performance status and hepatic metabolic function. However, there has never been a convincing survival advantage to chemotherapy demonstrated in a large, randomized trial. Therefore, chemotherapy cannot be considered the standard of care, and other approaches, including no active antineoplastic therapy, are reasonable and justified. The goal of therapy outside of a clinical trial setting must be palliation of symptoms attributable to the cancer. With the relatively low response rates seen in trials of chemotherapy in HCC, patients must be informed that the chance of meaningful symptom palliation is also low and may not justify the toxicity associated with the chemotherapy.

Many chemotherapeutic agents are metabolized by the liver; depending on the degree of hyperbilirubinemia, many patients may not be appropriate candidates for chemotherapy, or they may require dose reduction.

Performance status is an important issue to consider when counseling a patient regarding chemotherapy. The Zubrod (also referred to as ECOG [Eastern Cooperative Oncology Group]) and Karnofsky scales are

the two primary measures used to quantitate performance status (Table 1). Patients with a Zubrod score of 3 or 4 or a Karnofsky score of < 50% are usually not good candidates for chemotherapy, primarily because they are unable to tolerate chemotherapy-associated toxicities. Also, studies have consistently shown that patients with relatively good performance status have a greater chance of responding to chemotherapy than patients who are more debilitated. Most chemotherapy studies will not enroll patients with a Zubrod score > 2, and some require a score of 0 or 1.

Most chemotherapy drugs, when given systemically, cause myelosuppression with varying degrees of neutropenia, anemia, and thrombocytopenia. Patients with portal hypertension due to cirrhosis often have anemia that is multifactorial in etiology prior to starting chemotherapy, and support with red cell transfusions and/or recombinant erythropoietin may be necessary during chemotherapy. Often these patients have preexisting thrombocytopenia due to hypersplenism and other causes, and worsening thrombocytopenia during chemotherapy can place them at significant risk for bleeding. Febrile neutropenia is one of the most serious and most common toxicities associated with chemotherapy. Patients who have severe cytopenias at baseline are poor candidates for chemotherapy.

The overall response rates observed with chemotherapy in HCC have been relatively low compared with results in other tumors. The modest activity of chemotherapy is likely due in large part to an inherent resistance of HCC cells to chemotherapy drugs. Multidrug resistance genes and TP 53 (tumor suppressor) gene mutations are common in advanced HCC.^{1,2}

Single-Agent Chemotherapy

Many chemotherapeutic drugs have been tested as single agents in HCC. The anthracycline doxorubicin, which works through DNA intercalation as well as inhibition of topoisomerase II and formation of oxygen free radicals, has consistently demonstrated objective response rates (ORRs) in the 10 to 20% range and has long been considered one of the most active single drugs in this disease. Doxorubicin undergoes extensive hepatic metabolism and often requires dose reduction

or discontinuation in hyperbilirubinemic patients. Because of its ability to induce a dilated cardiomyopathy, usually in patients who have received high cumulative doses, careful evaluation of left ventricular ejection fraction is necessary before beginning treatment and periodically thereafter. Liposomal doxorubicin avoids much of the cardiotoxicity associated with standard doxorubicin but has not demonstrated equivalent response rates³ and is associated with other prominent toxicities, notably palmar-plantar erythrodysesthesia ("hand-foot syndrome"). Epirubicin and mitoxantrone are two other anthracycline drugs related to doxorubicin. Studies of these agents have not demonstrated superior response rates compared with doxorubicin.⁴⁻⁷

Fluorouracil (5-FU) and related agents, known collectively as the fluoropyrimidines, are also commonly used in hepatocellular carcinoma. They work through inhibition of the enzyme thymidylate synthase, as well as through incorporation of their metabolites into both DNA and RNA. As 5-FU has been found to be one of the most active agents in several types of gastrointestinal malignancies, it has undergone extensive evaluation in HCC. With rare exception, response rates to 5-FU have generally been shown to be in the range of $\leq 10\%$.⁸⁻¹⁰ Toxicities often include diarrhea, stomatitis, and some myelosuppression, as well as a hand-foot syndrome seen with the infusional schedules. 5-FU is given by many different schedules, including by bolus at different intervals as well as by continuous infusion. In an effort to increase convenience, oral fluoropyrimidine preparations have been developed, with capecitabine the only one approved for use in the United States. Capecitabine is a prodrug that is converted through hepatic metabolism and an enzymatic step at the site of tumor to 5-FU. Therefore, in contrast to most chemotherapy agents, capecitabine is designed to deliver chemotherapy in a more targeted fashion at the sites of tumor. Response rates have been found to be similar to 5-FU.¹¹ Like infusional 5-FU, capecitabine often causes a hand-foot syndrome, which can be extremely painful and dose-limiting. Diarrhea and stomatitis are also fairly common.

Cisplatin is a platinum analog that covalently binds to DNA and forms cross-links either within strands or between strands. When used systemically as a single agent in HCC, it has been shown to have a modest response rate of about 15%.¹² It has been studied more extensively in combination with other systemic agents, as well as in the intra-arterial setting.

Other cytotoxic chemotherapeutic agents that have either not been extensively tested as single agents or have not shown significant activity in HCC include the antimicrotubule taxane drugs (paclitaxel and docetaxel), topoisomerase I inhibitors (topotecan and irinotecan), topoisomerase II inhibitor (etoposide), and antimetabolite nucleoside analogues (such as gemcitabine and cladribine).

Combination Chemotherapy

Several different combinations of chemotherapy drugs have been studied. Although the response rates in some of the single-arm studies have been high enough to warrant further study, no combination to date has been proven to have superior activity compared with single agents. When considering a combination chemotherapy approach, it is important for clinicians to weigh the increased toxicity that is normally encountered when multiple toxic agents are combined against any added palliative benefit they may hope to achieve.

A recently reported study of cisplatin together with capecitabine and doxorubicin showed a 26% ORR, with 33% of patients exhibiting a $> 50\%$ decline in α -fetoprotein (AFP) levels.¹³ It should be noted that AFP decline has not been proven to be a reliable surrogate marker for any type of clinical benefit; however, many recent studies of systemic therapy in HCC are now using AFP decrease as a secondary study end point. Also, there is little mention of toxicity in the report of this study, other than there was one treatment-related death out of 25 treated patients. A phase II study of cisplatin plus doxorubicin showed an ORR of 19%, with 32% of the patients having a $> 50\%$ decrease in AFP levels.¹⁴ This study reported a severe neutropenia rate of 14.3%, which many oncologists would consider acceptable for a combination regimen. A phase II study of cisplatin plus gemcitabine showed an ORR of 21%, with a 32% rate of AFP reductions $> 50\%$.¹⁵ However, this study reported a 30% rate of severe neutropenia and 25% chance of severe thrombocytopenia, both of which are concerning in this patient population. A phase II study of infusional 5-FU, mitoxantrone, and cisplatin showed an ORR of 27%, but was associated with a very high (71%) rate of severe neutropenia.¹⁶ A combination of docetaxel plus gemcitabine showed only a 10% ORR along with unacceptable hematologic toxicity.¹⁷

Intra-Arterial Chemotherapy

Hepatic arterial infusion of chemotherapy attempts to take advantage of the fact that HCC cells derive most of their blood supply from the arterial circulation, in contrast to normal hepatocytes, which derive most of their blood supply from the portal venous circulation. Also, administering drugs that undergo a high degree of first-pass hepatic metabolism via a regional approach can potentially decrease systemic toxicity. Higher concentrations of chemotherapy at the site of tumor can be achieved in this manner. Complications related to the delivery catheter, such as dislodgement, are sometimes seen. Recent infusional protocols have utilized surgically implanted infusion pumps for drug delivery. Care must be taken by the surgeon to ligate branches of the hepatic artery feeding the gastrointestinal tract, or severe ulcerations can occur. Biliary toxicity, including sclerosing

cholangitis, is possible but has been seen with <10% frequency with newer regimens.¹⁸ Many studies have included patients with portal vein tumor thrombus.

Most hepatic arterial chemotherapy regimens include either cisplatin, doxorubicin, or mitomycin-C, which works primarily through alkylating and cross-linking DNA strands. A Korean study of a 5-day regimen of cisplatin plus 5-FU showed a 20% ORR with minimal systemic toxicity, but catheter-related complications occurred in 6 of 20 patients (30%).¹⁹ A Chinese study of a 5-day regimen of cisplatin, mitomycin C, the reduced folate drug leucovorin, and 5-FU reported a 28% ORR without severe toxicity.²⁰ A retrospective review of 23 cases at the University of Southern California utilizing a regimen of cisplatin plus mitomycin-C showed an ORR of 36% without any severe reported toxicities.²¹ Without large, randomized studies, it is impossible to know whether hepatic arterial infusion of chemotherapy offers any real clinical benefit compared with either systemic therapies or supportive care alone.

HORMONAL THERAPY

HCC cells sometimes express both wild-type and variant forms of estrogen receptors (ERs),^{22,23} and therefore there is a theoretical rationale for studying hormonal therapies. However, two large randomized trials have shown no evidence of a survival benefit for tamoxifen.^{24,25} Megestrol acetate, which blocks both wild-type and variant forms of ERs, has shown some evidence of activity in a small randomized study of patients whose tumors expressed variant ERs²⁶; this drug is currently being evaluated in a multicenter phase III trial. HCCs have also been shown to express androgen receptors.²⁷ However, studies of luteinizing hormone-releasing hormone (LHRH) agonists combined with antiandrogens have shown no evidence of benefit.^{28,29}

Octreotide is a somatostatin analogue that is often used in the treatment of carcinoid syndrome as well as other conditions. Because HCC cells are known to sometimes express somatostatin receptors,³⁰ octreotide has been studied as a therapy for HCC. One phase III study performed in Greece did report a statistically significant survival advantage for octreotide compared with no treatment³¹; however, another trial using long-acting octreotide failed to confirm this benefit.³²

In summary, there has been no clear evidence that any hormonal therapy is associated with a clinical benefit in HCC, although the role of megestrol acetate needs to be further defined in a large randomized study.

IMMUNOTHERAPY

Interferons are commonly used to treat hepatitis B and hepatitis C infections, and they appear to have some antiproliferative effects on hepatocytes³³ as well as dem-

onstrate immunomodulatory effects. Interferon-alpha has been the most studied in HCC. It is associated with significant systemic toxicities, including fatigue, myalgias, depression, elevation of hepatic transaminases, and leukopenia. Despite some promising small studies, larger studies have failed to confirm a benefit for interferon-alpha given as a single agent.³⁴ It has also been studied in combination with several different chemotherapeutic agents, including cisplatin, anthracyclines, and 5-FU. One phase III study from Korea of interferon-alpha plus cisplatin versus no treatment did report a statistically significant survival advantage (8 versus 3 months, $p=0.001$).³⁵ However, no other adequately powered study has indicated an advantage in terms of clinical benefit in favor of interferon plus chemotherapy versus chemotherapy alone. The 4-day PIAF regimen, which includes cisplatin, interferon-alpha, 5-FU, and doxorubicin, has been compared in a phase III study to doxorubicin alone with no significant difference seen in median survival or ORR.³⁶

Thalidomide is an oral agent that initially generated interest as an antineoplastic due to its known antiangiogenic properties,^{37,38} but it has also been found to have effects on cytokine production and immune function.³⁹ Its true mechanism of action remains unknown. It has shown some clinical activity in several tumor types and has become a standard treatment for multiple myeloma. Common toxicities associated with thalidomide include fatigue, peripheral neuropathy, venous thrombosis, and constipation. A phase II study in HCC evaluated high doses of thalidomide as a single agent, starting at 400 mg/d and escalating to 1000 mg/d by the fifth week. The ORR was only 5%, but the authors emphasized the 31% stable disease rate, a statistic that is frequently cited in studies of newer, noncytotoxic therapies.⁴⁰ However, the systemic toxicity of thalidomide at the dosage studied was prohibitive. A phase II study of thalidomide in combination with the anthracycline epirubicin showed no objective responses but had a stable disease rate of 41%.⁴¹ In this study, the median tolerated dose of thalidomide was 200 mg daily, which is consistent with its usage in other tumor types. Whether thalidomide will be shown to have a role in the treatment of HCC remains to be seen.

Several other immunotherapeutic agents are being studied in either preclinical or early phase clinical trials and will not be covered here. In summary, there is no clear evidence of a clinical benefit for interferon-alpha in HCC either as a single agent or in combination with chemotherapy. We await trials evaluating other immunotherapeutic agents.

TARGETED AGENTS

The intracellular Ras-anchoring protein plays a key role in cell signaling and proliferation, and Ras mutations are

overexpressed in many solid tumors including HCC. The hydroxy-methylglutaryl coenzyme A reductase inhibitor pravastatin has been shown to have activity as an inhibitor of farnesyl transferase, an enzyme that plays a key role in anchoring Ras to the cell membrane. Although a small study did not show a significant benefit,⁴² a phase III trial of pravastatin in advanced HCC is underway.

A small proportion (17%) of HCCs has been shown to overexpress epidermal growth factor receptor (EGFR). There is little preclinical evidence for activity of EGFR inhibitors in HCC, and no clinical studies have as yet been reported for these agents.

Many other novel, targeted agents are in development or are being tested in small studies in HCC. Although no targeted agent has yet been proven to have significant clinical benefit in HCC, the success of these strategies in other tumor types will no doubt lead to large trials of various targeted agents in this disease.

CHEMOTHERAPY AND OTHER SYSTEMIC THERAPIES FOR LIVER METASTASES

Several types of cancer commonly metastasize to the liver. Although some patients with liver metastases present with no other organ involvement and may be candidates for local therapeutic approaches, the majority of patients with liver metastases have widespread metastatic disease involving other organs. Chemotherapy, sometimes along with novel targeted therapies, is the mainstay of treatment for these patients. For most types of widely metastatic cancer, cure is not possible and the goals of therapy are palliation of symptoms and possibly prolongation of survival.

Colorectal Cancer

Colorectal cancer is the second most common cause of cancer death in the United States. Surgical resection of the primary tumor is the main treatment for early stage tumors. Adjuvant chemotherapy, to decrease the risk of recurrence, is generally offered to patients with pathological evidence of regional lymph node involvement as well as some node-negative patients who present with high-risk features such as bowel obstruction or perforation.⁴³

For patients who either present with metastatic disease initially or recur at distant sites, the liver is the most common site of metastasis. The main goal of following patients who have a history of colorectal cancer is to hopefully detect liver or other metastases at an early stage, when local therapy such as surgical metastatectomy may be feasible. Some patients who undergo metastatectomy will remain free of disease long term.⁴⁴ Because the liver is often the first site of recurrence, a local approach such as metastatectomy offers the possi-

bility of eradicating disease before other organs become involved. Neoadjuvant (preoperative) chemotherapy to decrease the size of liver metastases^{45,46} is a promising approach that can potentially improve resectability.

For patients who present with widespread metastatic disease or in those whose liver metastases are deemed unresectable, systemic therapy has long been the standard. 5-FU-based regimens have been widely used, with ORRs generally around 15 to 20%, and a median overall survival (MS) of 12 to 13 months.^{47,48} For many years, no regimen was proved superior to 5-FU, either in bolus regimens combined with leucovorin (LV) or in infusional regimens. Adding irinotecan to a 5-FU/leucovorin regimen was shown in two studies to be better in terms of ORR (39 and 49% in the two studies versus 21 and 22% for 5 FU/LV) and median survival (14.8 and 17.4 versus 12.6 and 14.1 months) compared with 5-FU/leucovorin alone.^{47,49} The platinum analog oxaliplatin was also added to 5-FU/LV (the FOLFOX regimen), and a large United States trial showed superiority of this regimen (ORR 45%, MS 19.5 months) compared with an irinotecan + 5-FU/LV regimen (ORR 31%, MS 15 months), as well as the combination of oxaliplatin + irinotecan (ORR 35%, MS 17.4 months).⁵⁰ The FOLFOX regimen, which utilizes infusional 5-FU along with bolus LV and oxaliplatin on a 48-hour schedule, therefore became the new standard for treating metastatic disease, with a median survival approaching 20 months. A cold-induced sensory neuropathy is a toxicity that is often dose-limiting with oxaliplatin. Irinotecan plus 5-FU/LV is still widely used, but the combinations with bolus 5-FU have been deemed excessively toxic due to a high incidence of severe diarrhea; infusional regimens (FOLFIRI [folinic acid, fluorouracil, and irinotecan], others) are preferred. Capecitabine has been shown to have equivalent ORRs and MS compared with 5-FU/LV, with the advantages of more convenience and a superior safety profile.⁵¹ In the metastatic setting, capecitabine has also been substituted for 5-FU/LV in combination with both oxaliplatin and irinotecan, with promising preliminary results.^{52,53}

Further progress in the field has continued with the addition of targeted biologic agents to cytotoxic chemotherapy. There has been great interest in targeted biologic agents as a means to improve the efficacy of chemotherapy while adding little toxicity. Cetuximab, a monoclonal antibody that targets the extracellular domain of the EGFR receptor, showed an ORR of 10.8% in irinotecan-refractory patients, which was increased to 22.9% when combined with irinotecan in this same patient population.⁵⁴ Toxicities of cetuximab are generally mild and reversible, including a diffuse skin rash that seems to correlate somewhat with response.⁵⁵ Although MS was not statistically different in the two groups, the higher ORR in the cetuximab (+) irinotecan group indicates that cetuximab may help overcome

resistance in chemorefractory patients. Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), has been added to irinotecan plus 5-FU/LV in previously untreated patients, with an MS of 20.3 months versus 15.6 months in the control group and a higher ORR (44.8 versus 34.8%).⁵⁶ Also, a recently presented study indicates that the addition of bevacizumab to FOLFOX improves MS (12.9 versus 10.8 months and ORR (21.8 versus 9.2 months) among patients who have progressed on first-line chemotherapy.⁵⁷ Toxicities noted with bevacizumab have included hypertension, proteinuria, vascular thrombosis, and, rarely, bowel perforation. Combining cetuximab with bevacizumab has shown promise in early studies, either with or without concurrent irinotecan.⁵⁸

Hepatic artery infusional (HAI) chemotherapy has been studied more extensively in colorectal cancer than in any other tumor type. The main reason for this is that colorectal cancer, especially when it involves the colon and not the rectum, typically exhibits a pattern of stepwise metastasis, with the liver being the first organ involved due to portal venous drainage of the colon. Many of the theoretical advantages for HAI in the setting of liver metastases are the same as in HCC, as noted above. Liver metastases derive the majority of their blood supply from the arterial circulation and are therefore preferentially exposed to the effects of HAI chemotherapy; hepatocytes rely mainly on the portal venous circulation.⁵⁹ Floxuridine (FUDR) is a fluoropyrimidine analog related to 5-FU that undergoes extensive first-pass hepatic metabolism, which makes it ideal for use in HAI regimens. Randomized studies of HAI chemotherapy versus systemic chemotherapy have consistently shown response rates in the range of 42 to 62% for infusional therapy, generally higher than the systemic arms of these trials.⁶⁰⁻⁶² The time to progression has also been consistently longer with HAI therapy in these trials. An overall survival benefit, however, has not been clearly demonstrated. Some argue that methodological issues, particularly the allowance of crossover to HAI therapy in many of the trials, have obscured a survival advantage.⁶³ The development of systemic metastases is a frequent problem among patients being treated with HAI chemotherapy, and combinations of HAI together with systemic therapy are being evaluated.

Breast Cancer

Breast cancer is the most commonly diagnosed cancer and the second most common cause of cancer death among women in the United States. The main treatment modalities for metastatic breast cancer include chemotherapy, hormonal therapy, and targeted therapy with the anti-Her-2/neu monoclonal antibody trastuzumab.

For patients whose tumor expresses either estrogen receptors, progesterone receptors, or both, initial

hormonal therapy is often preferred due to its favorable toxicity profile compared with chemotherapy. However, the slower time to response with hormonal agents often limits their use to patients who either have no visceral metastases or those who have visceral metastases that are felt not likely to be life-threatening over the course of 2 to 3 months. Response rates for tamoxifen have been noted between approximately 17 and 50%^{64,65} and ORRs for other hormonal agents are similar or slightly better.⁶⁶⁻⁶⁸ The hormonal agents used include the mixed estrogen receptor agonist/antagonists tamoxifen and toremifene; the aromatase inhibitors anastrozole, letrozole, and exemestane; and the pure antiestrogen fulvestrant. The progestin medroxyprogesterone acetate is still used in some situations but its relatively high risk of vascular thrombosis as well as fluid retention has limited its usefulness.

There are no large differences between these various hormonal agents in terms of ORRs and time to progression, and the choice of which agent to use first is generally made on the basis of relative toxicity profiles. The aromatase inhibitors are widely used in the first-line setting, with lower rates of vascular thrombosis and endometrial cancer than tamoxifen. There is, however, concern about the risk of osteoporosis with these agents and bone density scanning is required. Although most hormonal therapies are administered orally, fulvestrant is given via a monthly intramuscular injection. Other hormonally based approaches to patients whose tumors express hormone receptors are surgical oophorectomy, ovarian ablation via radiotherapy, and medical ovarian suppression with an LHRH analogue.

Chemotherapy is used in patients who have hormone-receptor-negative tumors, who fail to respond or who progress on hormonal treatments, or who have visceral organ involvement that threatens to cause organ dysfunction within a short period of time. Combination chemotherapy has been shown to produce higher ORRs, in excess of 70% in some studies,⁶⁹ but overall survival does not appear to be different than treatment with sequential single-agent therapy⁷⁰ and combination chemotherapy is associated with more toxicity. However, for patients who have significant visceral disease and require a rapid response, combination chemotherapy may be preferred. Chemotherapeutic agents commonly used as single agents include the anthracyclines, capecitabine, the taxanes, and the antimicrotubule agent vinorelbine. There are several possible combinations of these drugs; also, the DNA alkylating agent cyclophosphamide and 5-FU are added to some combination regimens. Combinations of two drugs are most common, but three-drug combinations are also used.

Targeted therapy with the monoclonal antibody trastuzumab is often used, either as a single agent or in combination with chemotherapy, in patients whose tumors overexpress the Her-2/neu protein. As a single

agent, the ORR is 26%⁷¹ and is in the range of 50% when added to chemotherapy.⁷² Trials targeting other pathways, including anti-VEGF therapy and anti-EGFR approaches, are currently underway.

HAI in patients with liver-only metastases has been evaluated in breast cancer. Several agents, including the antimicrotubule agent vinblastine, cisplatin, mitomycin-C, and FUDR, have been utilized. ORRs ranging from 19 to 81% have been reported.^{73,74} No randomized studies have been published comparing this approach to systemic therapy. Because there are a number of active systemic treatment options in breast cancer and because it is more rare than in colon cancer to have a patient with liver-only metastases, HAI therapy is rarely utilized in clinical practice.

Lung Cancer

Lung cancer is the second most commonly diagnosed type of cancer in both men and women and is now the leading cause of cancer-related mortality in both men and women in the United States. The main pathological categories are small-cell and non-small-cell lung cancer. Small-cell lung cancer is a neuroendocrine tumor that is highly chemosensitive, although it has a propensity to metastasize early in its course. The non-small-cell category includes squamous cell carcinoma, adenocarcinoma, and large cell anaplastic carcinoma, and although it is less chemosensitive than small-cell cancer, it is more often cured by surgical resection in its earliest stages. Both types carry a poor prognosis once metastatic, with median survival less than 1 year. Metastasis to the liver is a frequent finding.

For small-cell lung cancer, combination chemotherapy with a platinum analogue (cisplatin or carboplatin) plus etoposide remains the standard of care in the United States. A Japanese study has indicated that a combination of irinotecan plus cisplatin might be superior, but these results have yet to be confirmed.⁷⁵ For non-small-cell cancer, platinum-based combination chemotherapy has been the predominant therapy, with several studies demonstrating a modest survival advantage compared with supportive care alone.^{76,77} Recently, the addition of bevacizumab to carboplatin plus paclitaxel was reported to prolong survival compared with the two chemotherapy agents alone.⁷⁸ Also, the EGFR tyrosine kinase inhibitor erlotinib has been shown to prolong survival in patients who had failed two prior chemotherapy regimens.⁷⁹

Pancreatic Cancer

Pancreatic cancer is the fourth most common cause of cause of cancer deaths in both men and women in the United States. Over 95% of pancreatic cancers are adenocarcinomas, which are rarely diagnosed prior to

becoming locally advanced or metastatic. The most common site of metastasis is the liver. The standard treatment for metastatic pancreatic cancer has been single-agent chemotherapy with gemcitabine, which was shown to improve symptoms and quality of life versus single-agent 5-FU in a randomized trial.⁸⁰ To measure the quality-of-life benefit, the trial utilized a combined end point of pain (pain intensity and analgesic consumption), performance status, and weight and showed that 23.8% of patients in the gemcitabine arm received "clinical benefit" versus 4.8% in the 5-FU arm. One-year survivals were 18% versus 2% in favor of gemcitabine. The objective response rate in both arms was low (5.4% versus 0% in favor of gemcitabine). Several subsequent trials have failed to show an advantage to adding other chemotherapy agents to gemcitabine. A recently reported study did show a very modest improvement in overall survival with the addition of erlotinib to gemcitabine when compared with gemcitabine alone, with a 1-year survival rate of 24% versus 17%.⁸¹

CONCLUSIONS

Hepatocellular carcinoma and liver metastases both remain very difficult challenges for oncologists, although in some areas progress is gradually being made. Targeted biologic agents have demonstrated some promise in certain situations, and as these agents are further studied and improved upon, there is hope that systemic therapy will be much more effective and more tolerable for patients.

REFERENCES

1. Park JG, Lee SK, Hong IG, et al. MDR1 gene expression: its effect on drug resistance to doxorubicin in human hepatocellular carcinoma cell lines. *J Natl Cancer Inst* 1994;86:700-705
2. Park NH, Chung YH, Youn KH, et al. Close correlation of p53 mutation to microvascular invasion in hepatocellular carcinoma. *J Clin Gastroenterol* 2001;33:397-401
3. Valle JW, Dangoor A, Beech J, et al. Treatment of inoperable hepatocellular carcinoma with pegylated liposomal doxorubicin: results of a phase II study. *Br J Cancer* 2005;92:628-630
4. Hochster HS, Greeni MD, Speyer J, et al. 4'-Epidoxorubicin (epirubicin): activity in hepatocellular carcinoma. *J Clin Oncol* 1985;3:1535-1540
5. Pohl J, Zuna I, Stremmel W, et al. Systemic chemotherapy with epirubicin for treatment of advanced or multifocal hepatocellular carcinoma. *Chemotherapy* 2001;47:359-365
6. Dunk AA, Scott SC, Johnson PJ, et al. Mitoxantrone as single agent therapy in hepatocellular carcinoma: a phase II study. *J Hepatol* 1985;1:395-404
7. Colleoni M, Nole F, Di Bartolomeo M, et al. Mitoxantrone in patients affected by hepatocellular carcinoma with unfavorable prognostic factors. *Oncology* 1992;49:139-142
8. Tetef M, Doroshow J, Akman S, et al. 5-Fluorouracil and high-dose calcium leucovorin for hepatocellular carcinoma: a phase II trial. *Cancer Invest* 1995;13:460-463

9. Link JS, Bateman JR, Paroly WS, et al. 5-Fluorouracil in hepatocellular carcinoma: report of twenty-one cases. *Cancer* 1977;39:1936-1939
10. Porta C, Moroni M, Nastasi G, et al. 5-Fluorouracil and d,l-leucovorin calcium are active to treat unresectable hepatocellular carcinoma patients: preliminary results of a phase II study. *Oncology* 1995;52:487-491
11. Lozano RD, Patt YZ, Hassan MM, et al. Oral capecitabine (Xeloda) for the treatment of hepatobiliary cancers (hepatocellular carcinoma, cholangiocarcinoma, and gallbladder cancer) (abstract 1025). Paper presented at Annual Meeting of the American Society of Clinical Oncology; May 20-23, 2000; New Orleans, LA
12. Okada S, Okazaki N, Nose H, et al. A phase 2 study of cisplatin in patients with hepatocellular carcinoma. *Oncology* 1993;50:22-26
13. Shin D, Lee S, Park J, et al. Systemic chemotherapy with capecitabine, doxorubicin and cisplatin for metastatic hepatocellular carcinoma (abstract 4177). Paper presented at Annual Meeting of the American Society of Clinical Oncology; May 13-17, 2005; Orlando, FL
14. Lee J, Park JO, Kim WS, et al. Phase II study of doxorubicin and cisplatin in patients with metastatic hepatocellular carcinoma. *Cancer Chemother Pharmacol* 2004;54:385-390
15. Yang TS, Chang WC, Lin YC, et al. A phase II study of gemcitabine and cisplatin for patients with advanced hepatocellular carcinoma (abstract 1351). Paper presented at Annual Meeting of the American Society of Clinical Oncology; May 31-June 3, 2003; Chicago, IL
16. Ikeda M, Okusaka T, Ueno H, et al. A phase II trial of continuous-infusion 5-fluorouracil, mitoxantrone and cisplatin for metastatic hepatocellular carcinoma (abstract 4081). Paper presented at Annual Meeting of the American Society of Clinical Oncology; June 5-8, 2004; New Orleans, LA
17. Kim GP, Alberts SR, Tschetter LK, et al. Gemcitabine and docetaxel in patients with measurable unresectable or metastatic hepatocellular carcinoma, a North Central Cancer Treatment Group (NCCTG) phase II trial (abstract 4270). Paper presented at Annual Meeting of the American Society of Clinical Oncology; June 5-8, 2004; New Orleans, LA
18. Kemeny N, Kemeny M, Lawrence TS. Liver metastases. In: Abelloff M, Armitage J, Niederhuber J, Kastan M, McKenna WG, eds. *Clinical Oncology*. Philadelphia: Elsevier Churchill Livingstone; 2004:1141-1178
19. Jang BK, Kwon KM, Chung WJ, et al. Efficacy of hepatic arterial infusion therapy for advanced hepatocellular carcinoma using 5-fluorouracil and cisplatin. *Korean J Hepatol* 2004;10:271-278
20. Lin CP, Yu HC, Cheng JS, et al. Clinical effects of intra-arterial infusion chemotherapy with cisplatin, mitomycin C, leucovorin and 5-fluorouracil for unresectable advanced hepatocellular carcinoma. *J Chin Med Assoc* 2004;67:602-610
21. Ru J, Byone S, Nelson T, et al. Hepatic intra-arterial infusion (HIA) of cisplatin and mitomycin-C for hepatocellular carcinoma: the USC experience (abstract 1519). Paper presented at Annual Meeting of the American Society of Clinical Oncology; May 31-June 3, 2003; Chicago, IL
22. Jonas S, Bechstein WO, Heinze T, et al. Female sex hormone receptor status in advanced hepatocellular carcinoma and outcome after surgical resection. *Surgery* 1997;121:456-461
23. Villa E, Colantoni A, Grottola A, et al. Variant estrogen receptors and their role in liver disease. *Mol Cell Endocrinol* 2002;193:65-69
24. Chow PK, Tai BC, Tan CK, et al. High-dose tamoxifen in the treatment of inoperable hepatocellular carcinoma: a multicenter randomized controlled trial. *Hepatology* 2002;36:1221-226
25. Perrone F, Gallo C, Daniele B, et al. Tamoxifen in the treatment of hepatocellular carcinoma: 5-year results of the CLIP-1 multi-centre randomized controlled trial. *Curr Pharm Des* 2002;8:1013-1019
26. Villa E, Ferretti I, Grottola A, et al. Hormonal therapy with megestrol in inoperable hepatocellular carcinoma characterized by variant oestrogen receptors. *Br J Cancer* 2001;84:881-885
27. Negro F, Papotti M, Pacchioni D, et al. Detection of human androgen receptor mRNA in hepatocellular carcinoma by in situ hybridization. *Liver* 1994;14:213-219
28. Grimaldi C, Bleiberg H, Gay F, et al. Evaluation of antiandrogen therapy in unresectable hepatocellular carcinoma: results of a European Organization for Research and Treatment of Cancer multicentric double-blind trial. *J Clin Oncol* 1998;16:411-417
29. Manesis EK, Giannoulis G, Zoumboulis P, et al. Treatment of hepatocellular carcinoma with combined suppression and inhibition of sex hormones: a randomized, controlled trial. *Hepatology* 1995;21:1535-1542
30. Reubi JC, Zimmermann A, Jonas S, et al. Regulatory peptide receptors in human hepatocellular carcinomas. *Gut* 1999;45:766-774
31. Kouroumalis E, Skordilis P, Thermonths K, et al. Treatment of hepatocellular carcinoma with octreotide: a randomised controlled study. *Gut* 1998;42:442-447
32. Yuen MF, Poon RT, Lai CL, et al. A randomized placebo-controlled study of long-acting octreotide for the treatment of advanced hepatocellular carcinoma. *Hepatology* 2002;36:687-691
33. Radaeva S, Jaruga B, Hong F, et al. Interferon-alpha activates multiple STAT signals and down-regulates c-Met in primary human hepatocytes. *Gastroenterology* 2002;122:1020-1034
34. Llovet JM, Sala M, Castells L, et al. Randomized controlled trial of interferon treatment for advanced hepatocellular carcinoma. *Hepatology* 2000;31:54-58
35. Ji SK, Park NH, Choi HM, et al. Combined cis-platinum and alpha interferon therapy of advanced hepatocellular carcinoma. *Korean J Intern Med* 1996;11:56-68
36. Yeo W, Zee B, Leung WT, et al. A phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil combination chemotherapy for inoperable hepatocellular carcinoma (abstract 4026). Paper presented at Annual Meeting of the American Society of Clinical Oncology; June 5-8, 2004; New Orleans, LA
37. Vacca A, Ribatti D, Roncali L, et al. Bone marrow angiogenesis and progression in multiple myeloma. *Br J Haematol* 1994;87:503-508
38. Rajkumar SV, Fonseca R, Witzig TE, et al. Bone marrow angiogenesis in patients achieving complete response after stem cell transplantation for multiple myeloma. *Leukemia* 1999;13:469-472
39. Argiles JM, Carbo N, Lopez-Soriano FJ, et al. Was tumour necrosis factor-alpha responsible for the fetal malformations associated with thalidomide in the early 1960s? *Med Hypotheses* 1998;50:313-318
40. Patt YZ, Hassan MM, Lozano RD, et al. Thalidomide in the treatment of patients with hepatocellular carcinoma: a phase II trial. *Cancer* 2005;103:749-755

41. Zhu AX, Fuchs CS, Clark JW, et al. A phase II study of epirubicin and thalidomide in unresectable or metastatic hepatocellular carcinoma. *Oncologist* 2005;10:392-398
42. Lersch C, Schmelz R, Erdmann J, et al. Treatment of HCC with pravastatin, octreotide, or gemcitabine: a critical evaluation. *Hepatogastroenterology* 2004;51:1099-1103
43. Benson AB III, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol* 2004; 22:3408-3419
44. Fernandez FG, Drebin JA, Linehan DC, et al. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with fluorodeoxyglucose (FDG-PET). *Ann Surg* 2004;240: 438-447
45. Gruenberger T, Schuell B, Kornek G, et al. Elderly patients do benefit from oxaliplatin based neoadjuvant chemotherapy in resectable colorectal cancer liver metastases (abstract 3601). Paper presented at Annual Meeting of the American Society of Clinical Oncology; May 13-17, 2005; Orlando, FL
46. Bathe OF, Ernst S, Sutherland F, et al. A phase II study of neoadjuvant irinotecan, 5-fluorouracil and leucovorin for resectable liver metastases from colorectal cancer (abstract 3662). Paper presented at Annual Meeting of the American Society of Clinical Oncology; May 13-17, 2005; Orlando, FL
47. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000;343:905-964
48. Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998;16:301-308
49. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomized trial. *Lancet* 2000;355:1041-1047
50. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004;22:23-30
51. Twelves C. Capecitabine as first-line treatment in colorectal cancer: pooled data from two large, phase III trials. *Eur J Cancer* 2002;38:S15-S20
52. Cassidy J, Tabernero J, Twelves C, et al. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. *J Clin Oncol* 2004; 22:2084-2091
53. Grothey A, Jordan K, Kellner O, et al. Randomized phase II trial of capecitabine plus irinotecan versus capecitabine plus oxaliplatin as first-line therapy of advanced colorectal cancer (abstract 1022). Paper presented at Annual Meeting of the American Society of Clinical Oncology; May 31-June 3, 2003; Chicago, IL
54. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; 351:337-345
55. Susman E. Rash correlates with tumour response after cetuximab. *Lancet Oncol* 2004;5:647
56. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335-2342
57. Giantonio BJ, Catalano PJ, Meropol NJ, et al. High-dose bevacizumab improves survival when combined with FOL-FOX-4 in previously treated advanced colorectal cancer: results from the Eastern Cooperative Oncology Group study E3200 (abstract 2). Paper presented at Annual Meeting of the American Society of Clinical Oncology; May 13-17, 2005; Orlando, FL
58. Lenz H-J, Hochster H, Wadler S, et al. Randomized phase II trial of cetuximab/bevacizumab/irinotecan versus cetuximab/bevacizumab in irinotecan-refractory colorectal cancer (abstract 3508). Paper presented at Annual Meeting of the American Society of Clinical Oncology; May 13-17, 2005; Orlando, FL
59. Breedis C, Young C. The blood supply of neoplasms in the liver. *Am J Pathol* 1954;30:969-985
60. Hohn D, Stagg R, Friedman M, et al. A randomized trial of continuous intravenous versus hepatic intra-arterial floxuridine in patients with colorectal cancer metastatic to the liver: The Northern California Oncology Group Trial. *J Clin Oncol* 1989;7:1646-1654
61. Chang AE, Schneider PD, Sugarbaker PH, et al. A prospective randomized trial of regional versus systemic continuous 5-fluorouridine chemotherapy in the treatment of colorectal liver metastases. *Ann Surg* 1987;206:685-693
62. Martin J, O'Connell MG, Wieland HS, et al. Intra-arterial floxuridine versus systemic fluorouracil for hepatic metastases from colorectal cancer: a randomized trial. *Arch Surg* 1990; 125:1022-1027
63. Kemeny N, Kemeny M, Lawrence T. Liver metastases. In: Abelloff M, Armitage J, Niederhuber J, Kastan M, McKenna W, eds. *Clinical Oncology*. Philadelphia: Elsevier Churchill Livingstone; 2004:1141-1178
64. Muss HB, Case LD, Atkins JN, et al. Tamoxifen versus high-dose oral medroxyprogesterone acetate as initial endocrine therapy for patients with metastatic breast cancer: a Piedmont Oncology Association study. *J Clin Oncol* 1994;12:1630-1638
65. Manni A, Trujillo JE, Marshall JS, et al. Antihormone treatment of stage IV breast cancer. *Cancer* 1979;43:444-450
66. Nabholz JM, Buzdar A, Poltak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *J Clin Oncol* 2000; 18:3758-3757
67. Bonnetterre J, Thurlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the tamoxifen or arimidex randomized group efficacy and tolerability study. *J Clin Oncol* 2000;18:3748-3757
68. Mouridsen H, Gershonovich M, Sun Y, et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 2001;19:2596-2606
69. Nabholz JM, Mackey JR, Smylie M, et al. Phase II study of docetaxel, doxorubicin, and cyclophosphamide as first-line chemotherapy for metastatic breast cancer. *J Clin Oncol* 2001; 19:314-321
70. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol* 2003;21: 588-592

71. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002;20:719-726
72. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783-792
73. Frascini G, Fleishman G, Yap H-Y, et al. Percutaneous hepatic arterial infusion of cisplatin for metastatic breast cancer. *Cancer Treat Rep* 1987;71:313-315
74. Arai Y, Sone Y, Inaba Y, et al. Hepatic arterial infusion chemotherapy for liver metastases from breast cancer. *Cancer Chemother Pharmacol* 1994;33(suppl):142-144
75. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small cell lung cancer. *N Engl J Med* 2002;346:85-91
76. Gridelli C. The ELVIS trial: a phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer. *Elderly Lung Cancer Vinorelbine Italian Study*. *Oncologist* 2001;6(suppl 1):4-7
77. Gridelli C, Aapro M, Ardizzoni A, et al. Treatment of advanced non-small-cell lung cancer in the elderly: results of an international expert panel. *J Clin Oncol* 2005;23:3125-3137
78. Sandier AB, Gray R, Brahmer J, et al. Randomized phase II/III trial of paclitaxel plus carboplatin with or without bevacizumab in patients with advanced non-squamous non-small cell lung cancer: an Eastern Cooperative Oncology Group trial-E4599 (abstract LBA4). Paper presented at Annual Meeting of the American Society of Clinical Oncology; May 13-17, 2005; Orlando, FL
79. Shepherd FA, Pereira J, Ciuleanu TE, et al. A randomized placebo-controlled trial of erlotinib in patients with advanced non-small cell lung cancer following failure of first or second line chemotherapy: a National Cancer Institute of Canada Clinical Trials Group trial (abstract 7022). Paper presented at Annual Meeting of the American Society of Clinical Oncology; June 5-8, 2004; New Orleans, LA
80. Bums HA III, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403-2413
81. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared to gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group (abstract 1). Paper presented at Annual Meeting of the American Society of Clinical Oncology; May 13-17, 2005; Orlando, FL