Surg Oncol Clin N Am
12 (2003) 127–134

SURGICAL
ONCOLOGY
CLINICS OF
NORTH AMERICA

Are there indications for chemotherapy in hepatocellular carcinoma?[1]

Philip J. Johnson, MD, FRCP*

Division of Cancer Studies, School of Medicine, University of Birmingham, United Kingdom

A recent review by European experts stated that "The activity of chemotherapy in patients with hepatocellular carcinoma (HCC) is negligible" [1]. There are many in oncology that would agree and would therefore answer the question posed in the title of this article in the negative.

The first aim of this article is to examine the literature on the utility of systemic chemotherapy as assessed by conventional oncologic response criteria. Second, the article examines the way in which physicians currently assess the efficacy of treatment for HCC, and liver tumors in general, showing that such practices are questionable. Despite the quotation referred to in the first paragraph, the same review also noted that "measurement of tumour load by bi-dimensional measurement is not accurate enough . . . extensive tumour necrosis may not be paralleled by a reduction in tumour volume" [1]. Third, how physicians assess the impact of new treatments on survival, when many of the patients have an additional, potentially fatal condition (chronic liver disease) with an independent natural history, is also considered.

It is widely held that surgical resection is the definitive treatment for HCC and the only one that offers the hope of cure or, at least, long-term survival; however, most patients have unresectable disease at presentation because of poor liver function (about 75% of patients have underlying chronic liver disease), bilobar disease, or extrahepatic metastases. The overall resectability rate for HCC is thus only 10% to 25%. If the disease is unresectable, the prognosis is poor, with an overall median survival of only a few months.

* Institute of Cancer Studies, University of Birmingham, Edgbaston, Vincent Drive, Birmingham B15 2TT, United Kingdom.

[1] This article is from a talk given at the American Association of Clinical Oncology, May 2002.

E-mail address: johnsonp@cancer.Dham.ac.uk

PII: S 1 0 5 5 - 3 2 0 7 (0 2) 0 0 0 7 5 - 3

Even among those who undergo surgical resection, there is a recurrence rate of up to 83% at 5 years [2–6].

For patients with unresectable disease or postoperative recurrence, nonsurgical treatment is instigated, usually with palliative intent. Nonsurgical treatment can be locoregional, including intra-arterial treatment or percutaneous local ablative treatments, and there is some evidence that some forms of percutaneous ablative therapy, such as percutaneous alcohol injection, may be as effective as surgery [7,8]. When regional lymph nodes are involved or there are extrahepatic metastases, locoregional treatment is not indicated; intra-arterial treatment is also contraindicated when there is involvement of the main portal venous system. For patients who are unsuitable for any of the previously described treatments, systemic chemotherapy is usually considered.

This introduction to HCC treatment brings out three points to consider when asking whether chemotherapy is indicated for HCC:

- Only patients with very advanced disease are entered into studies of systemic therapy. The combination of high tumor load, poor performance status, and widespread disease are all factors that, in oncologic practice, are associated with poor response to chemotherapy.
- Patients with HCC usually have underlying chronic liver disease:
  - This may affect the efficacy of drugs used to treat HCC systemically.
  - Survival figures may be influenced as much by the severity of the underlying liver disease as by the course of the HCC. Thus, ''cure'' of the HCC may only have a small impact on survival.
- It is not certain that even if responses could be induced by systemic chemotherapy, physicians are using the correct methods for detecting them.

Systemic cytotoxic chemotherapy for hepatocellular carcinoma

HCC is widely considered to be chemotherapy resistant. Response rates for single-cytotoxic-agent chemotherapy, as assessed by conventional criteria, are low, and durable remission is rare. From 1973 to 1986, response rates were reported at around 20%; since 1993, reported response rates have been lower, often 0% (Table 1) [9]. The most commonly used single cytotoxic agent for HCC has been Adriamycin (doxorubicin), an anthracycline. In a review of 13 published trials by Nerenstone et al [10], the response rate was about 20% with a median survival time of 4 months. Complete remissions have occasionally been described. A prospective trial that randomized 60 patients to receive either Adriamycin or no active treatment reported an increase in survival from a median value of 7 weeks for the control arm to 11 weeks for the Adriamycin arm, despite a reported death rate of 25% caused by complications of the Adriamycin administration [11]. In a systematic review of five other randomized trials using Adriamycin therapy, no significant survival effect was discernable [12]. The dose-limiting toxicity

Table 1
Single-agent response rates for hepatocellular carcinoma

Investigators	Drug	No. patients	Objective response rate, % (CR and PR)
Damrongak et al, 1973	Vinblastine	25	8
Johnson et al, 1978	Adriamycin	44	32
Chlebowski et al, 1984	Adriamycin	52	11
Melia et al, 1983	VP-16	24	13
Hochster et al, 1985	4′-epidoxorubicin	18	17
Dunk et al, 1985	Mitoxantrone	22	27
Falkson et al, 1987	Cisplatin	35	17
Lin et al, 1993	Ifosfamide	17	0
Chao et al, 1998	Paclitaxelfrom	20	0
Ruff et al, 1998	Clofazimine	30	10
Mok et al, 1999	Nolatrexed	37	0
Yeo et al, 1999	Liposomal daunorubicin	14	0
Lozano et al, 2000	Capecitabine	37	13

Abbreviations: CR, complete response; PR, partial response.
Data from: Heneghan MA, O'Grady JG. Liver transplantation of malignant liver disease. Ballieres Clin Gastroenterol 1999;13:575–91.

of Adriamycin is mainly cardiac and bone marrow suppression; deaths caused directly from Adriamycin toxicity are extremely rare.

Treatment with Adriamycin is relatively contraindicated in patients with concomitant heart disease, and the dosage should be reduced if liver function is poor (total bilirubin more than twice the upper limit of the reference range). From the trials reported previously, if there is no improvement in symptoms, tumor size, or the serum α-fetoprotein (AFP) level, treatment should be stopped.

Combination chemotherapy

Combination chemotherapy appears to give a higher response rate (Table 2), though again the duration of remission is short [10]. It is also difficult to compare activity among different regimens as most trials were single-arm phase II studies and response criteria were not consistent. In general, even for well-selected patients, the expected objective response for combination chemotherapy is only around 20% to 30%. Any improvement in response rate over systemic therapy may simply be attributable to the better performance status of patients who are entered into trials with more aggressive chemotherapy.

These data show that single-agent Adriamycin gives a response rate of around 15% to 20% and, with combination therapy, this figure rises to around 20% to 35%. Nonetheless, HCC is clearly not entirely chemotherapy resistant, although there is no proven efficacy in survival improvement [13]. The response rate for Adriamycin is similar to that of many other widely used chemotherapeutic agents, such as 5-fluorouracil, in metastatic gastrointestinal cancer and liver metastases.

Table 2
Combination chemotherapy response rates for hepatocellular carcinoma

Investigators	Drug	No. patients	Objective response rate, % (CR and PR)
Al-Idrissi et al, 1982	Adriamycin, 5-FU, mitomycin C	40	13
Falkson et al, 1984	Adriamycin, 5-FU, MeCCNU	38	21
Ravry et al, 1984	Adriamycin, bleomycin	60	16
Patt et al, 1993	5-FU, interferon	28	18
Porta et al, 1995	5-FU, leucovorin	25	28
Ji et al, 1996	Cisplatin, interferon alpha-2b	30	13.3
Bobbio-Pallavicini et al, 1997	4′-epidoxorubicin, etoposide	36	39
Urabe et al, 1998 (intra-arterial)	Methotrexate, 5-FU, cisplatin, interferon alpha-2b	16	46.7
Leung et al, 1999	Cisplatin, 5-FU, Adriamycin, interferon alpha-2b	50	26

Abbreviations: 5-Fu, 5-fluorouracil; CR, complete response; PR, partial response.
Data from: Heneghan MA, O'Grady JG. Liver transplantation of malignant liver disease. Ballieres Clin Gastroenterol 1999;13:575–91.

Antihormonal therapy

An alternative systemic approach has been endocrine manipulation. Early small-scale studies with antiestrogenic and antiandrogenic agents showed some promise [14]; however, recent large-scale prospective controlled studies have largely refuted any role for antiandrogenic agents or tamoxifen [15–17]. In a recent small-scale prospective controlled study, octreotide led to a significant improvement in survival (13 months in the treated group versus 4 months in the control group). Although there were no reported "responses," octreotide appears worthy of larger-scale studies [18].

Assessing response to systemic chemotherapy

There are now several reports in the literature that suggest that the standard radiologic criteria for assessment of response (bidimensional measurement) may not tell the whole story in the case of liver tumors [19].

Experience from the PIAF regimen

Most single-agent and combination chemotherapy trials have used conventional response criteria as the primary end point; complete remission has been rarely reported. For those patients who achieved partial response, there is little information on the histology of the treated lesion because tissue examination is rarely undertaken. However, Patt et al [20] used a four-drug systemic intra-arterial combination chemobiotherapy of cisplatin, recombinant interferon alpha-2b, Adriamycin, and 5-fluorouracil (PIAF) and reported a complete pathologic remission in a patient with disseminated HCC.

A phase II study, using the same drug combination but modified to an outpatient intravenous treatment, involved 50 patients with unresectable HCC and reported an objective response rate of 26% (all partial responses) [21]. Although the response rate was not high, 9 of the 13 partial responders had their disease rendered operable. Pathologic examination of the resected specimens confirmed complete pathologic remission in four patients. The same group has recently updated their results and reported 15 cases (including the 9 cases reported earlier) of unresectable HCC that underwent surgical resection for the residual lesion after partial response to PIAF [22]. There were 8 complete pathologic remissions of the 15 cases and, in the remainder, there was more than 95% necrosis. Most of the cases were American Joint Committee on Cancer stage IV disease (12 of 15), with a median tumor diameter of 7.4 cm (range, 3.9 to 22 cm). There were two deaths of 50 patients in the PIAF trial, both caused by neutropenic sepsis.

It is important not to overinterpret the results of these studies and to recognize their several limitations. Thus, this regimen has not yet been subjected to a prospective randomized trial and experience is largely confined to those with hepatitis B–related HCC. This regimen is associated with considerable hematologic toxicity. In addition, claims for increased rates of "resectability" should be read cautiously; criteria are not absolute, and there is considerable variation in the opinion of surgeons as to what constitutes "resectability."

Nonetheless, there are important lessons to be drawn from experience with the PIAF regimen, and the following conclusions appear warranted:

- Conversion to resectable disease and complete pathologic remission are possible after aggressive systemic combination chemotherapy alone, even in the case of large, unresectable HCC.
- Conventional radiologic assessment of response does not necessarily reflect the true extent of tumor cell kill. Normalization of serum AFP after treatment may be a better indicator of response, and the inclusion of serum AFP changes as a response criterion in phase II trials for HCC should be considered.
- Previous phase II studies that used simple bidimensional tumor measurement may have underestimated the activity of the agents under investigation.

Other evidence that conventional response criteria for liver tumors may not be ideal

Following several types of treatment in patients with hepatic metastases, no change in the size of the liver defects on CT scanning was noted, although at the time of exploration, no viable tumor cells were found in the liver [19,23]. Lau et al [24] had a similar experience in patients with HCC treated by selective internal radiation therapy using yttrium-90 microspheres. Response rates to radiotherapy, measured by the decrease in tumor markers, were much higher

than those based on changes in tumor size/volume as assessed by CT images and, as with the PIAF regimen, partial responses on conventional criteria have, in some cases, proved to show complete pathologic remission on examination following surgical resection [24].

Experience in treating liver metastases from gastrointestinal stromal tumors with the tyrosine kinase inhibitor ST1571 has also shown that evidence of cell kill can long precede any change in liver tumor size and that techniques such as MRI and positron emission tomography scanning may be required for early detection of the agent's efficacy [25].

Who responds to systemic chemotherapy?

Because only a minority of patients with HCC responds to systemic chemotherapy and the treatment is toxic, it would be useful to predict, prior to treatment, which patients would be the best candidates for PIAF or Adriamycin therapy. In a multivariate analysis of 149 patients with unresectable HCC and treated with PIAF, it was found that good liver function, indicated by a lower serum bilirubin and absence of cirrhosis, was associated with a response rate of 50% [26]. This is in accord with a much earlier study in which a normal bilirubin level was also associated with a much higher response to systemic Adriamycin [27]. These observations deserve further follow-up. Aside from their obvious clinical application, they may also account for the apparent decrease in response to systemic therapy over recent decades. A reasonable explanation would be that with the introduction of new treatments such as intra-arterial and percutaneous ablative therapies, which are now widely perceived to be the standard therapy for patients with inoperable disease, systemic therapy is currently given to patients in much poorer condition than they were in earlier years. This may account for the poor response rates recently reported; it may also mean that physicians are getting an inaccurate picture of the efficacy of drugs in phase II studies.

The impact of underlying chronic liver disease on survival

Because of the difficulty in assessing response to treatment, it is tempting to suggest that improvement in survival as assessed in controlled trials might be a more meaningful measure of drug efficacy. Even this approach, however, is problematic.

Liver function clearly is a major determinant of prognosis (as distinct from response) in patients with HCC. Certainly, measures of liver function outweigh "tumor-related" factors in most staging/prognostic systems [28]. Thus, it is possible that any beneficial effect a drug has on decreasing tumor cell mass may be undetectable, because the patient's prognosis/survival is mainly determined by his or her underlying liver function [29]. Furthermore, because patients with worse liver function are now entered into clinical trials

of systemic therapy, this too limits the extent to which any therapy can improve survival.

Summary

Single-agent Adriamycin gives a response rate of around 15% to 20%, and with combination therapy, this figure rises to around 20% to 35%; however, there is no proven survival benefit. Nonetheless, HCC is clearly not entirely chemotherapy resistant and complete pathologic remission is possible after systemic combination chemotherapy alone. Major methodologic problems remain in assessment of response and the survival benefit from systemic therapy. Until these are resolved, the answer to the question posed in this article is unknown; further appropriate studies remain to be undertaken.

References

[1] Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference [European Association for the Study of the Liver]. J Hepatol 2001;35:421–30.
[2] Nagao T, Panis Y, Farges O, et al. Intrahepatic recurrence after resection of hepatocellular carcinoma complicating cirrhosis. Ann Surg 1991;241:114–7.
[3] Nagao T, Inoue S, Yoshimi F, et al. Post operative recurrence of hepatocellular carcinoma. Ann Surg 1990;211:28–33.
[4] De Matteo RP, Fong Y, Blumgart LH. Surgical treatment of malignant liver tumours. Ballieres Clin Gastroenterol 1999;13:557–74.
[5] Heneghan MA, O'Grady JG. Liver transplantation of malignant liver disease. Ballieres Clin Gastroenterol 1999;13:575–91.
[6] Nagasue N, Uchida M, Makino Y, et al. Incidence and factors associated with intrahepatic recurrence following resection of hepatocellular carcinoma. Gastroenterology 1993; 105:488–94.
[7] Castells A, Bruix J, Bruc C, et al. Treatment of small hepatocellular carcinoma in cirrhotic patients: a cohort study comparing surgical resection and percutaneous ethanol injection. Hepatology 1993;18:1121–6.
[8] Yamamoto J, Okada S, Shimada K, et al. Treatment strategy for small hepatocellular carcinoma: comparison of long-term results after percutaneous ethanol injection therapy and surgical resection. Hepatology 2001;34:707–13.
[9] Leung WT, Johnson PJ. Systemic therapy for hepatocellular carcinoma. Semin Oncol 2001;28:514–29.
[10] Nerenstone SR, Ihde DC, Friedman MA. Clinical trials in primary hepatocellular carcinoma: current status and future directions. Cancer Treat Rev 1988;15:1–31.
[11] Lai CL, Wu PC, Chan GC, et al. Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. Cancer 1988;62:479–83.
[12] Simonetti RG, Leberati A, Angiolini C, et al. Treatment of hepatocellular carcinoma: a systematic review of randomized controlled trials. Ann Oncol 1997;8:117–36.
[13] Mathurin P, Rixe O, Carbonell N, et al. Overview of medical treatments in unresectable hepatocellular carcinoma—an impossible meta-analysis? Aliment Pharmacol Ther 1998; 12:111–26.
[14] Chow PKH, Soo KC. Hormonal therapy in hepatocellular carcinoma. The current scientific and clinical evidence. Am J Surg 2000;23:56–63.

[15] CLIP Group. Tamoxifen in the treatment of hepatocellular carcinoma: a randomised controlled trial. Lancet 1998;352:17–20.
[16] Castells A, Bruix J, Bru C, et al. Treatment of hepatocellular carcinoma with tamoxifen: a double-blind placebo-controlled trial in 120 patients. J Gastroenterol 1995;109:917–22.
[17] 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;16:411–7.
[18] Kouroumalis E, Skordilis P, Thermos K, et al. Treatment of hepatocellular carcinoma with octreotide: a randomised controlled study. Gut 1998;42:442–7.
[19] Barone RM, Byfield JE, Goldfarb PB, et al. Intra-arterial chemotherapy using an implantable infusion pump and liver irradiation for treatment of hepatic metastases. Cancer 1982;50:850–4.
[20] Patt YZ, Hoque A, Roh M, et al. Durable clinical and pathologic response of hepatocellular carcinoma to systemic and hepatic arterial administration of platinol, recombinant interferon alpha 2B, Adriamycin, and 5-fluorouracil: a communication. Am J Clin Oncol 1999;22:209–13.
[21] Leung TWT, Patt YZ, Lau WY, et al. Complete pathological remission is possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. Clin Cancer Res 1999;5:1676–81.
[22] Lau WY, Leung WT, Lai BS, et al. Pre-operative systemic chemoimmunotherapy and sequential resection for unresectable hepatocellular carcinoma. Ann Surg 2001;233:236–41.
[23] Nauta RJ, Herees EK, Thoms DS, et al. Intraoperative single-dose radiotherapy. Observations on staging and interstitial treatment of unresectable liver metastases. Arch Surg 1987;122:1392–5.
[24] Lau WY, Ho S, Leung WT, et al. Selective internal radiation therapy for inoperable hepatocellular carcinoma with intraarterial infusion of yttrium^{90} microspheres. Int J Rad Oncol Bio Phys 1998;40:583–7.
[25] Hoensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N Engl J Med 2001;344:1052–6.
[26] Leung TWT, Tang AMY, Zee B, et al. Factors predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, Adriamycin and 5-fluorouracil (PIAF) chemotherapy. Cancer 2002; 94:421–7.
[27] Johnson PJ, Alexopoulos AT, Johnson RD, et al. Significance of serum bilirubin in response of hepatocellular carcinoma to Adriamycin. J Hepatol 1986;3:149–53.
[28] Johnson PJ. Hepatocellular carcinoma. In: Gospodarowicz MK, Henson DE, Hutter RVP, et al, editors. Prognostic factors in cancer. 2nd edition. New York: Wiley-Liss; 2001. p. 297–310.
[29] Bruix J. Treatment of hepatocellular carcinoma. Hepatology 1997;25:259–62.