HPB, 2005; 7: 50–55

Taylor & Francis
Taylor & Francis Group

Non-surgical treatment of hepatocellular carcinoma

PHILIP J. JOHNSON

Cancer Research UK Institute for Cancer Studies, University of Birmingham, UK

Abstract
A wide variety of non-surgical therapies can result in clinical responses in patients with hepatocellular carcinoma. Two recent studies have suggested that transarterial chemoembolisation can, in highly selected patients with good liver function, result in an improvement in survival. No other approaches have, to date, demonstrated convincing evidence of survival advantage.

Key words: *Hepatocellular carcinoma; intra-arterial chemotherapy; chemoembolisation; ablative therapy; radiotherapy; systemic chemotherapy; biotherapy*

Introduction

Surgical resection is currently considered to be the definitive treatment for hepatocellular carcinoma (HCC) and the only one that offers the prospect of cure or at least long-term survival. However, most patients have unresectable disease at presentation because of poor liver function (about 75% will have underlying chronic liver disease), bilobar disease, invasion of the major vessels or overt extrahepatic metastases. The overall resectability rate for HCC is thus only 10–25% and even among those who undergo surgical resection with curative intent, there is a recurrence rate of up to 80% at 5 years [1–3]. More recently there have been suggestions that other therapeutic modalities such as percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) are also potentially "curative". It should be noted that the term "curative" in this sense is usually meant to imply "resulting in complete local control of the original lesion". Cure in the strict and true sense of the word is seldom achieved.

Where conventional surgical resection is contraindicated because of poor underlying liver function, orthotopic liver transplantation is an option, particularly for those who have small tumours [4–6] but again recurrence remains a possibility and shortage of donor livers means that many will succumb while awaiting transplantation. It is thus apparent that the majority of patients with HCC will, at some point during the course of their disease, be candidates for non-surgical therapy. It is also apparent that they represent, by virtue of whatever factors preclude them for surgical resection, a relatively poor risk group.

Non-surgical treatment can be classified as locoregional, including intra-arterial or percutaneous local ablative approaches, a combination of the two, or systemic. When regional lymph nodes are involved or there are extrahepatic metastases, locoregional treatment is seldom indicated. Intra-arterial treatment is also contraindicated when there is involvement of the main portal venous system. Systemic chemotherapy is usually considered for the patients who are unsuitable for any of the above treatments.

It should be emphasized from the start that "liver failure" as indicated by overt jaundice, recurrent or diuretic-resistant ascites, recurrent gastrointestinal haemorrhage or encephalopathy unexplained by other factors will, in the view of most authorities, preclude any form of active treatment other than liver transplantation. In such patients prognosis is primarily defined by the underlying liver function rather than the tumour; effective anti-tumour therapy may not necessarily improve overall survival. Figures will vary from unit to unit and around the world but as a very broad generalization 15% of patients will be considered for surgical resection, 50% for non-surgical therapies and 35% will be unsuitable for any active treatment, and will receive best supportive care. These figures will change as more patients are detected in the asymptomatic stage by screening.

Intra-arterial and regional drug delivery

With the disappointing results seen with systemic therapy, several approaches that aim to target the tumour specifically have been developed. There are two ways in which targeting may be achieved. The first approach is based on the observation that primary and secondary liver tumours derive the bulk of their blood

Correspondence: P. J. Johnson, Institute of Cancer Studies, Vincent Drive, Edgbaston, Birmingham, UK. Tel: +44 121 414 3801. Fax: +44 121 414 4486. E-mail: p.johnson@bham.ac.uk

ISSN 1365-182X print/ISSN 1477-2574 online
DOI: 10.1080/13651820410024076

supply from the hepatic artery [7]. This approach to selectivity may be further enhanced by new arteriographic procedures that permit "super selective" catheterization of the tumour-feeding artery. Direct infusion of cytotoxic agents into the hepatic artery may allow an increase of the exposure of the tumour to the drug. Depending on the agent used, the time/concentration interval may increase by up to 400-fold. Dose-limiting toxicity may then become "regional" (i.e. hepatic and not systemic) [8–11].

A second source of selectivity is the use of lipiodol as a vehicle for cytotoxic chemotherapy. This oily based contrast medium, when injected into the hepatic artery at the time of arteriography, is cleared from normal hepatic tissues but accumulates in malignant tumours, probably because of the leaky character of neovascular tissue, combined with the lack of lymphatic clearance from tumour tissue [12]. The lipiodol forms an emulsion with the cytotoxic agent and then acts as a reservoir for the prolonged delivery of the agent to the tumour, and perhaps enhances uptake by the tumour cells. The extent to which the lipiodol acts as an embolizing agent in itself remains controversial.

There seems no doubt that, compared with systemic administration [13–15], drugs given intra-arterially are more effective, although it must not be forgotten that patients treated in this manner invariably have a better performance status than those treated with systemic therapy. For this reason, better results would be expected regardless of any inherent increased efficacy of the treatment.

Transcatheter oily chemoembolization (TACE)

Following hepatic angiography to identify the arterial anatomy and the blood supply of the tumour a catheter is placed in the appropriate vessel. Not infrequently angiography identifies tumour not detected by CT scanning. In the past the entire liver has been covered by placement of the catheter in the proper hepatic artery but nowadays it is more common to use the left or right hepatic artery when the whole of one lobe is involved, or, where feasible, to selectively catheterize just the tumour-feeding arteries, and the procedure becomes "segmental". The cytotoxic drug (usually doxorubicin or cisplatin) is mixed with lipiodol and the emulsion is injected slowly. Finally, embolization with 0.5–1 mm of gelatin cubes or a similar material is undertaken [16].

The presence of Child's grade C cirrhosis is usually considered to be a contraindication, as is thrombosis of the portal vein, because the cirrhotic liver is crucially dependent on the hepatic artery in this situation, and any further interruption thereof may lead to liver failure. Thrombosis of the portal vein is also an indication of particularly bad prognosis and is associated with the development of extrahepatic disease. If the procedure is undertaken by an experienced interventional radiologist the mortality should be well below 5% and significant side effects are rare (1%) apart from occasional gallbladder infarction [17]. Effective embolization is often associated with the so-called "post embolization syndrome" of fever, pain and vomiting for up to a week, after which it subsides spontaneously. Significant deterioration in liver function may occur but usually only when Child's grade C patients are treated. Although widely regarded as standard treatment for almost 15 years, and clear evidence that tumour necrosis was indeed caused, early controlled trials did not show an increase in survival and the consensus was that although the "primary effect" (i.e. causing tumour volume reduction) is good, there is little effect on long-term survival for which other factors such as the tumour type, degree of spread and serum alpha-fetoprotein (AFP) level are more significant than the treatment [18–21].

However, more recently, two trials and a systematic review have, for the first time, provided evidence that TACE may indeed improve survival, in selected cases. In the first of these Lo *et al.* randomized 80 subjects to either TACE (with cisplatin in lipiodol followed by gelatin sponge embolization) or best supportive therapy [22]. The survival figures at 1, 2 and 3 years were 57%, 31% and 26% compared with 32%, 11% and 3%, respectively ($p = 0.006$). In the second study, from Spain, 112 patients were randomized to TACE with doxorubicin again followed by gelfoam embolization, or best supportive therapy [23]. Survival figures at 1 and 2 years were 82% and 63% in the TACE group compared with 75% and 50% for embolization alone and 63% and 27% for those receiving best supportive therapy. In both studies the procedure was repeated if there was no evidence of progressive disease. The systematic review suggested that chemoembolization, either doxorubicin or cisplatin, but not embolization alone showed a significant benefit (2-year probability of survival, compared with control, odds ratio 0.53 with 95% confidence limits of 0.32–0.89). The systematic review again suggested that benefits were mainly in those with well preserved liver function (Child's grade A) and without vascular invasion [16].

While these two studies have, according to many authorities, established TACE as the standard of care for patients with larger HCCs, we should remain cautious. Both trials were small, and some criticisms about how well the treatment and control groups were balanced have been raised. Furthermore, and of particular importance in designing further comparative studies, there remains considerable controversy as to what is actually meant by the term "chemoembolization" and the relative importance of the "embolization" and the "chemotherapy" aspects of the treatment. It is notable that different cytotoxic agents were used in the two trials. Some in the field aim to develop extensive tumour necrosis by the embolization, while others use the embolic material to slow down the blood flow to the tumour and not to