LEADING ARTICLE

Hepatocellular carcinoma: is current therapy really altering outcome?

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Progress in the management of hepatocellular carcinoma (HCC) has been slow and has limited impact on outcome. Most patients with HCC have two diseases—chronic liver disease and HCC—and complex interactions between the two have major implications for diagnosis and prognosis as well as the management of HCC. The disease is most prevalent in those areas of the world where the infrastructure for clinical trials is least developed. Also, the aetiology of the disease varies around the world and it is still not known whether HCCs of different aetiologies have different prognoses. Current treatment is making an impact on the management of HCC but further progress awaits not only the development of more effective treatments but also the development of adequate methodologies to assess the impact of these treatments.

There can be no doubt that progress in the management of hepatocellular carcinoma (HCC) has been slow. An appreciation of the barriers faced by researchers in this area may however explain the limited impact on outcome and shed some light on the way forward. Firstly, most patients with HCC have two diseases—chronic liver disease, usually at the stage of cirrhosis, *and* HCC. The two diseases have complex interactions that have major implications for diagnosis and prognosis as well as the management of HCC. Secondly, the disease, among the most common cancers worldwide, is most prevalent in those areas of the world where the infrastructure for clinical trials is least developed. Thirdly, the aetiology of the disease varies around the world and it is still not known with any certainty whether HCCs of different aetiologies have different prognoses. Are the results of trials undertaken in one part of the world with its own aetiological agent applicable to other areas? Against this background it is perhaps not surprising that progress has been slow.

The first stage of assessing a patient with HCC is, apparently, simple. Is the tumour surgically resectable? If so, it is widely agreed, the patient should proceed to have the tumour removed. In the absence of any referral bias, 10–20% of patients will be accepted with a view to curative resection. Surgery is not possible more often for technical reasons (the lesion may be deeply placed or close to vital structures), or there are already overt extrahepatic metastases, the patient has comorbid medical conditions, or it is perceived that the patient's remaining liver will not support life. The normal liver regenerates rapidly even after removal of 75% of its mass but the cirrhotic liver does not regenerate as well and liver failure in the immediate postoperative period is an ever present threat. To compound matters, in the majority of cases, the tumour will "recur" after apparently successful resection and the patient will succumb.[1–4] None the less, the survival curves of surgical series appear to flatten out, suggesting that a small subset, probably approximately 5% of the whole group, is indeed cured. Surgical mortality has fallen over recent years and a value of less than 5% for patients without cirrhosis and 10% for those with cirrhosis should be achievable.[5] The decision as to whether or not the patient will survive resection because of impaired underlying liver function is often made fairly subjectively or following the simple guideline that patients with Child's grade A liver function are suitable, those with Child's C are not, and there is no clear indication for those with Child's grade B.

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Modest progress has been made in this subset of patients. The decrease in surgical mortality is clearly one area of progress that reflects both better supportive care and better surgical techniques. Commendable as such progress may be, one could still ask, "if surgical resection *is* the only hope of long term survival maybe patients would accept much higher values for operative risk?" Furthermore, there is now good evidence that there may be more rational indications of the likely success of surgical intervention. Bruix *et al* have provided evidence that portal hypertension and hyperbilirubinaemia are key factors that adversely impact on the likelihood of long term survival.[6] Postoperative adjuvant therapy that aims to decrease the rate of disease recurrence is an area of intense research and there have been a number of positive prospective randomised clinical trials (RCT). A recently reported RCT suggested that administration of a single dose of intrahepatic arterial lipiodol I^{131} (1850 MBq), after complete resection, significantly decreased the rate of recurrence

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Abbreviations: HCC, hepatocellular carcinoma; RCT, randomised clinical trial; TOCE, transcatheter oily chemoembolisation; AFP, α fetoprotein.

(from 59% to 28.5%) at three years, and increased the overall survival rate at three years from 46% to 86%.[7] Similar reductions in the recurrence rate have been reported with adoptive immunotherapy and by the use of the synthetic retinoid, polyprenoic acid, although in neither of these series was overall survival increased.[8 9]

If the reason for non-resectability is poor underlying liver dysfunction, then liver transplantation is the best approach.[10] Mazzaferro *et al* reported an actuarial survival rate of 75%, and an 83% disease free survival rate at four years.[11] This group of patients were required to have tumours smaller than 5 cm in diameter and less than three in number. If the patient has a smaller tumour, or the tumour is detected unexpectedly at the time of liver transplantation for end stage liver disease, the results are even better.

"All patients with HCC should be assessed to determine if their disease is resectable"

Clearly, all patients with HCC should be assessed to determine if their disease is resectable and it is important that this opinion be gained from a centre with extensive experience in liver surgery. If the disease is not operable on the grounds of underlying liver insufficiency, orthotopic liver transplantation should be considered where this is an available option. The question of transplantation for patients that have tumours that could be resected by conventional surgery remains controversial depending among other things on the availability of donors.[12–14]

If progress has been made, what question remains? No randomised controlled trial of surgery or transplantation has been undertaken. While it appears self evident that surgical resection, when successful, must be better than no treatment, a recent series from Spain described a group of patients with asymptomatic HCC without adverse risk factors (presumably not dissimilar to those undergoing surgical resection) in which overall median survival was over three years,[15] a value similar to that seen in some surgical series. None the less it seems unlikely that randomised trials will ever be undertaken; perhaps the most important question, referred to below, will be whether or not some locoregional therapies may perform as well as surgical resection.

TREATING UNRESECTABLE DISEASE

It has been conventional at this stage to draw a clear line between surgical removal (resection) of the tumour (or orthotopic liver transplantation) that are by intent curative, and all other approaches that are considered to be of palliative intent. These include so-called locoregional therapies and systemic therapies, although strictly speaking surgical resection is one form of locoregional therapy.

"Lipiodol has been used as a vehicle for targeting cytotoxic drugs"

When lipiodol, an oily contrast medium, is injected into the hepatic artery at the time of arteriography, subsequent computed tomography scanning shows that it is cleared from normal hepatic tissues but accumulates in malignant tumours. Lipiodol has therefore been used as a vehicle for targeting cytotoxic drugs. In so-called "transcatheter oily chemoembolisation" (TOCE) an attempt is made to enhance the effect of arterial embolisation by the addition of chemotherapy. Typically, 60 mg of doxorubicin are mixed with 15 ml of lipiodol and injected into the tumour feeding arteries. This is followed by embolisation with 0.5–1 mm of gelatin cubes. The procedure has been widely regarded as standard treatment for inoperable disease. Although there is tumour regression in more than 50% of cases, early prospective randomised trials did not confirm the efficacy of the procedure in terms of improvement in survival.[16 17] None the less, TOCE remained widely practised and proponents were unconvinced by the negative clinical trials, identifying within them several problems. The large number of participating centres, each contributing only a small number of patients, variation in operator technique, and extent of embolisation achieved were all concerns. Such concerns now appear to have been well founded as recently described clinical trials have both reported improvement in survival.[18 19] Of course, TOCE actually comprises at least two therapies—embolisation and chemotherapy—even if lipiodol itself is not considered therapeutic. The question of which is the "active" agent or whether it is the combination that is successful is an interesting question, particularly as embolisation on its own does not appear to prolong survival.[20]

"It seems likely that trials comparing surgery and ablative therapies will soon emerge"

There have been numerous other locoregional treatments described[21 22] including percutaneous ethanol injection,[23–25] thermal ablation,[26 27] and internal radiotherapy.[28] Whether or not any of these would also fare as well as TOCE under controlled conditions remains to be seen. None the less some are now being added to the list of "radical treatments" implying that either they may be curative or at least as good as surgery. As noted above it seems likely that trials comparing surgery and ablative therapies will soon emerge. The author's suspicion is that there will be little to choose in terms of survival advantage between the various regional approaches that seek to remove the tumour by physical means, be it surgery, TOCE, or any of the other locoregional therapies. Most likely the optimal treatment will be decided on the basis of cost, side effects, and quality of life assessment.

It is important to emphasise that all of these locoregional treatments appear to be most effective—and this was well illustrated in the two controlled trials of TOCE—in patients with small tumours, usually defined as less than 5 cm in diameter. We are therefore faced with an overabundance of treatment modalities all competing for a minority of patients. For the typical patient with a large tumour at presentation, improvements in outcome has been much more modest and most likely must await advances in systemic therapy.

SYSTEMIC THERAPY

HCC is widely considered to be chemotherapy resistant.[29] Response rates for single agent chemotherapy, usually doxorubicin, are approximately 15–20%.[30–32] Combination chemotherapy appears to give a higher response rate (20–30%) although in both cases remissions are usually short and survival advantage has not been convincingly demonstrated.[33]

"HCC is widely considered to be chemotherapy resistant"

None the less, HCC is clearly not entirely chemotherapy resistant and the response rate for doxorubicin is of the same order as many other widely used chemotherapeutic agents, such as 5-fluorouracil, in metastatic gastrointestinal cancer and liver metastases. Attempts to improve survival by hormonal manipulation using antiandrogens or antioestrogens, both of which appeared promising in several earlier studies, have now been well investigated in adequately powered randomised trials and found to be of no benefit.[34] A small randomised trial of the somatostatin analogue octreotide was positive and is worthy of further investigation.[35]

However, an emerging question is the extent to which current criteria are adequate for detecting response to systemic chemotherapy. The standard radiological criterion (bidimensional measurement) may not tell the whole story. For example, a recent study of combination therapy[36 37] reported an objective partial response rate (by conventional criteria) of approximately 20%. In several of these "partial responses" the patient's disease was rendered operable and pathological examination of the resected specimens confirmed complete pathological remission. The residual tumour identified on computed tomography scanning simply represented dead fibrous tissue. This experience shows that conversion to resectable disease and complete pathological remission *are* possible after aggressive systemic combination chemotherapy alone, even in the case of large unresectable HCCs, and that conventional radiological assessment of response does not necessarily reflect the true extent of tumour cell kill. Normalisation of serum α fetoprotein (AFP) after treatment may be a better indicator of response and inclusion of serum AFP changes as response criteria in phase II trials for HCC should be considered. It seems likely that previous phase II studies may have underestimated the activity of the agents under investigation.

As only a minority of patients respond to systemic therapy, and the treatment is toxic, it would be useful to be able to predict, prior to treatment, which patients would be most likely to respond to therapy. In a multivariate analysis of 149 patients with unresectable HCC and treated with combination chemotherapy, it was found that good liver function, as indicated by a low serum bilirubin, and absence of cirrhosis, were strongly associated with a higher response.[38] Indeed in those with a low bilirubin level and no cirrhosis, the response rate approached 50%. Interestingly, 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 doxorubicin.[39] As chemotherapy is usually used only in patients with advanced disease, when local therapies have either failed or are inappropriate, these observations may explain why the response rates to chemotherapy appear very low.

The impact of underlying chronic liver disease on survival

In view 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. However, even this approach is fraught with problems. It is clear that liver function is a major determinant of prognosis in HCC—measures of liver function outweigh "tumour related" factors in most staging/prognostic systems.[40] Thus it is possible that any beneficial effect a drug may have on decreasing tumour cell mass may be undetectable as the patient's prognosis/survival is mainly determined by his underlying liver function. Furthermore, and in conjunction with the points made in the previous paragraph, it should be noted that as patients with worse liver function are now entered into clinical trials of systemic therapy this too will limit the extent to which any effective therapy can be detected in clinical trials.

> "Liver function is a major determinant of prognosis in HCC"

As if these difficulties were not sufficient, the closely related problems of screening high risk populations for HCC with a view to early tumour detection is also a methodological minefield and one in which controlled trials are not likely to yield any helpful results. Current treatment *is* making an impact on the management of HCC but further progress awaits not only the development of more effective treatments but also the development of adequate methodologies to assess the impact of currently available treatment; until such have been defined, we will never know exactly how great is the impact of our therapeutic endeavours.

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