New medical options for liver tumours

Sarah Williams, Daniel Palmer and Philip Johnson

ABSTRACT – Significant progress is being made in the prevention of hepatitis B-related hepatocellular carcinoma (HCC) but hepatitis C-related HCC is increasing in the West and therapeutic advances in established disease have been modest. Although ablative therapies, including surgical resection, seem effective in patients with small tumours these only represent a minority of patients. For the majority with advanced disease there is some evidence for survival benefit for transarterial chemoembolisation but only in very carefully selected patients. Systemic chemotherapy is of unproven benefit and is now largely confined to clinical trials. In contrast, there has been a steady improvement in the outlook of patients with established metastatic liver cancer when the primary site is colorectal. Survival has increased from around six months to almost two years with the introduction of new cytotoxic agents, irinotecan and oxaliplatin. Somatostatin analogues have had a dramatic impact on the symptomatic control of neuroendocrine tumours, metastatic to the liver that result in the carcinoid syndrome.

KEY WORDS: carcinoid syndrome, chemoembolisation, chemotherapy, colorectal cancer, hepatocellular carcinoma, metastatic liver disease, somatostatin analogues

Introduction

The liver is the organ most often involved in malignant disease. In developing countries primary liver cancer (hepatocellular carcinoma (HCC)) is a major public health problem and responsible for over 500,000 deaths/year.[1] In the West the incidence of HCC is rising particularly in relation to the increasing prevalence of chronic hepatitis C virus (HCV) infection.[2] The liver is also the major site of secondary (metastatic) liver cancer, particularly from colorectal cancer (CRC) but also from several other primary tumours. After a brief overview of the epidemiology, presentation and diagnosis of liver tumours, this review aims to summarise the current state of, and recent advances in, the medical management of the major primary and secondary liver tumours for the general physician.

The risk factors for HCC development are now well known – chronic viral hepatitis types B or C (HBV and HCV), hepatic cirrhosis of any aetiology and, particularly in developing countries, exposure to the mould-derived toxin, aflatoxin.[3] In view of the possibility of identifying and screening high risk groups with the aim of early diagnosis and prevention, recognition of risk factors is of major importance especially due to the limited therapeutic options available. There is now emerging evidence that both vaccination at birth against, and antiviral treatment of, chronic HBV infection decrease the subsequent rate of HCC development.[4,5] Nonetheless, there is no prospect of a vaccine against HCV, and it will take at least 20 more years before HBV vaccination has a major impact on HCC incidence. Hepatocellular carcinoma will remain a very significant health problem for generations to come. Likewise, although early diagnosis of CRC by screening may decrease the number of cases presenting with advanced metastatic disease, liver involvement will remain a major clinical problem at some point in the natural history of the disease.

The importance of underlying chronic liver disease in hepatocellular carcinoma

The principles of managing liver tumours are similar between primary and secondary tumours with one fundamental exception: in HCC the underlying liver is seldom 'normal'. In at least 80% of cases there is chronic liver disease, usually at the stage of cirrhosis.[6] This affects the mode of presentation, complicates diagnosis and limits therapeutic options as outlined below.

Presentation

The vast functional reserve of the liver means that tumours can reach a considerable size before causing signs and symptoms, typically the triad of right upper quadrant pain, hepatomegaly and weight loss. In the case of HCC, decompensation of pre-existing chronic liver disease (recurrent variceal haemorrhage, development of diuretic resistant ascites or encephalopathy) is also a frequent presentation. Rarer presentations include haemoperitoneum and hypoglycaemia. The former comprises sudden onset of severe abdominal pain and shock, due to rupture of the tumour into the peritoneum; ascitic tap reveals

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blood-stained ascites. Obviously, in the case of metastatic disease the presence of the primary tumour will often be established before symptoms related to the liver develop. Increasingly, both primary and secondary tumours are being diagnosed at a pre-symptomatic stage as a result of surveillance programs. Most specialist units recommend six-monthly surveillance with ultrasound (US) examination and serum α-fetoprotein (AFP) measurement in patients known to have chronic liver disease and in whom early detection could reasonably be expected to lead to active treatment by resection, ablation or transplantation. Thus, surveillance of patients with end-stage liver disease would not be considered worthwhile as they would not be candidates for liver transplantation. The role of serum AFP in surveillance is being increasingly questioned as its sensitivity and specificity in patients with early disease is very low.

Diagnosis

If there is reason to suspect a liver lesion in patients with CRC, US examination is usually the first investigation. Definitive examination of suspicious lesions is either through CT or MRI scan and, in terms of assessment for suitability of resection, they both have a sensitivity and specificity of around 90%.[7] PET scanning is increasingly used in those who are deemed suitable for resection as it may detect extrahepatic metastases that were previously undiagnosed; this investigation will alter the management of patients in about 20–25% of cases.[8] Rising levels of carcinoembryoninc antigen levels after apparently successful resection of the primary lesion virtually always heralds tumour recurrence, usually in the liver. In the case of HCC either dynamic triphasic CT or gadolinium-enhanced MRI will classically show marked enhancement in the arterial phases with relative hypovascularity ('wash out') on the portal or late phases. If the lesion is above 2 cm in diameter, then two radiological studies consistent with HCC, or one together with an AFP level of >400 ng/ml, are considered sufficient to establish the diagnosis of HCC without recourse to liver biopsy in patients with chronic liver disease.[9] If these criteria are not met, the diagnosis requires histological confirmation although a surgical opinion should be sought prior to biopsy as many surgeons prefer to avoid biopsy of potentially operable lesions for fear of tumour seeding in the needle track or systemic dissemination.

Overall management plan

Once a diagnosis has been established the first question for all liver tumours is, 'is the tumour surgically resectable?' In the case of HCC, orthotopic liver transplantation is a further option particularly if there is severe underlying liver disease. Typically around 10–15% of cases are suitable and, in the cases of metastatic disease, UK guidelines have been published.[10] In many cases, however, there will be tumour recurrence after resection and such patients will eventually become candidates for medical management. Conventional wisdom is that surgical resection, although never the subject of a randomised controlled trial, is the only option associated with 'cure' or at least long-term survival, but the line between surgical and other approaches to tumour destruction is becoming blurred with the development of ablative therapies such as radiofrequency, microwave or cryoablation. The extent to which the results achieved by these approaches are equivalent to surgical resection, particularly in the case of HCC, is controversial. For the purposes of this review, however, it has been assumed that the essence of medical treatment is to have some aspect of a systemic approach and as such the various local therapies will not be discussed further.

Medical management of metastatic liver disease – a changing paradigm

The integration of systemic chemotherapy into the management of advanced cancer represents the first part of a paradigm shift in modern oncology and treatment options are now invariably planned in a multidisciplinary team setting. The bulk of research into medical management of liver metastases has been in the field of CRC since, unlike most other metastatic cancer, liver-confined disease occurs in a significant number of patients.

In patients with cancer, systemic chemotherapy has three distinct indications:

- as therapy for established, clinically evident metastatic disease to palliate symptoms and prolong survival
- in the adjuvant setting, to decrease the rate of recurrence after curative resection of the primary lesion. Essentially this is treatment of potential micrometastatic disease
- as therapy for established metastatic disease, with a view to 'downstaging' the disease so that resection may be successfully accomplished.

All these indications are relevant to liver metastases.

A second part of the paradigm shift is the move from 'non-specific' drugs (the classical cytotoxic agents) to rationally designed drugs aimed at targets that have been identified by an understanding of the underlying molecular pathology of the disease. Nonetheless, the backbone of management is 5-fluorouracil (5-FU), a classical cytotoxic drug that was rationally designed in the 1950s to interfere with DNA and RNA synthesis through inhibition of the enzyme thymidylate synthase (TS), and all the drugs that have had the major impact on survival improvement are still classical cytotoxic drugs. The newer molecular agents that are being introduced have impacted on survival, but it is their relative lack of toxicity rather than dramatic efficacy that is notable.

Thirdly, it is apparent that advances are made in a series of small steps rather than 'major breakthroughs'. Each step makes a very modest improvement in survival, typically in the order of a small number of months. In the case of metastatic CRC, however, when the whole picture is reviewed over a decade, it can be seen that median survival has increased from around six months to almost two years. Once activity has been demonstrated in the setting of established metastatic disease, research may take one of two directions. Firstly, effective regimens can be moved into the adjuvant setting. Secondly, there will be a spectrum of

response ranging from those with no evidence of response to those with 'complete response', ie disappearance of all macroscopic disease. The option of surgical resection arises among those who respond well to treatment. The current challenge is to use molecular biological techniques to predict, before treatment, which patient will respond and to which drug.

The backbone of chemotherapy for CRC is 5-FU. A recent meta-analysis has confirmed that the addition of folinic acid (FA) (also known as leukovorin) approximately doubles the response rate from 10% to 20% through stabilisation of the interaction of 5-FU with TS, but the consequent improvement in survival is marginal. Bolus 5-FU is more convenient; but prolonged infusion gives a slightly better response rate and less toxicity, again with only a small increment in survival.[11] This was the situation up until the 1990s when three new cytotoxic agents were introduced. Capecitabine is a fluoropyrimidine precursor that is converted to 5-FU by a series of enzymatic reactions. Unlike 5-FU, it is predictably orally bioavailable. It appears to be at least as effective as 5-FU, but avoids the need for infusion pumps and venous access. Although not exhaustively tested in direct comparative studies, capecitabine can probably substitute for 5-FU in combination regimens.

Irinotecan inhibits topoisomerase I, a DNA unwinding enzyme required for cell division. Irinotecan first demonstrated improved survival as a single agent compared to supportive care in patients with 5-FU refractory disease.[12] Randomised studies have now shown that when irinotecan is added to 5-FU/FA as a first line treatment there is a significant increase in median survival of around three months compared to 5-FU/FA alone.[13] Irinotecan can have significant toxicity manifesting in two forms. The first is gastrointestinal (GI) (diarrhoea, vomiting, and abdominal cramping) and the second vascular (acute myocardial infarction, pulmonary embolus and cerebrovascular accident). When the regimen was administered in combination with bolus 5-FU, fatal toxicity was as high as 5% compared to less than 1% in the control (5-FU/FA) arm. Using infusional regimens (so-called FOLFIRI ie FOLinic acid/Fluorouracil/IRinotecan by Infusion) the toxicity is tolerable if patients are carefully screened for pre-existing cardiovascular disease and any GI toxicity is aggressively managed.

Oxaliplatin is a diaminocylcohexane platinum derivative with a different spectrum of activity from the widely used cisplatin and carboplatin. It also has a different spectrum of toxicity with no renal and minimal hepatic toxicity but marked neurological toxicity – a 'glove and stocking' sensory deficit occurring in 15% of cases, which is cumulative but largely reversible upon cessation of treatment. In preclinical models there was activity against colon cancer cell lines and synergism with 5-FU. Phase II trials reported a 10–25% response rate as a single agent in metastatic colorectal cancer, but in combination with 5-FU this increased to 50%. Randomised trials of oxaliplatin plus 5-FU confirmed the high response rate of combination therapy but overall survival benefit was not achieved, in part due to 'crossover', in which a significant number of patients initially assigned to 5-FU alone subsequently received oxaliplatin.[14] In subsequent studies, oxaliplatin plus 5-FU showed at least equivalent activity to irinotecan-based regimens and 5-FU combined with either oxaliplatin or irinotecan can now be considered equivalent first line regimens.[15] Although evidence relating to the optimal chemotherapy schedule for CRC from randomised controlled trials is not available, the accumulated data suggest that exposure to all three classes of drug (fluoropyrimidine, oxaliplatin, and irinotecan) at some point in the course of the disease will optimise overall survival, with an improvement from six to nine months with 5-FU to almost two years when all active agents are exhibited.

More recently, two monoclonal antibodies, bevacizumab and cetuximab have been introduced. The former is a recombinant humanised monoclonal antibody that blocks the activity of vascular endothelial growth factor, and as such is postulated to have an antiangiogenic mode of action. Bevacizumab increased survival, when added to an irinotecan-based regimen by almost five months with a resultant median survival of over 20 months,[16] and when added to a 5-FU/FA regimen was as effective as irinotecan plus bolus 5-FU/FA.[17] The extent to which the benefits of bevacizumab are related to its antiangiogenic activity or its ability to increase blood flow through alterations in intratumoral interstitial pressure (and thereby increased chemotherapy delivery) to the tumour remains undetermined. Combination chemotherapy with bevacizumab now represents a standard treatment in the US and much of Europe but, to date, there is no provision for bevacizumab within the NHS.

Cetuximab, an antibody against the epidermal growth factor receptor (EGFR) has been licensed for the treatment of irinotecan-resistant disease. This is based on preclinical evidence that cetuximab can reverse resistance to irinotecan and on a randomised phase II trial reporting a response rate of 23% to the combination of cetuximab plus irinotecan compared to 11% for cetuximab alone in patients with irinotecan-refractory disease and EGFR-expressing tumours.[18] To date there are no data indicating improved survival with cetuximab, but trials investigating its addition to first line chemotherapy regimens are in progress.

'Downstaging' of liver metastases

As noted above, in about 15% of cases liver metastases appear confined to the liver and surgical resection leads to five-year survival in the order of 35–50%. The evidence is convincing that only surgical resection that can produce such figures, even though surgery has never been shown as better than either no active treatment or chemotherapy in a controlled trial. Since combination chemotherapy now consistently achieves responses in up to 50% of cases, the possibility of rendering initially unresectable disease resectable arises and there are now several series in which this has been achieved in up to 40% of cases.[19] The approach is, however, still in the early stages of development. It is clear that eventual recurrence is still the rule, and several other problems need to be addressed. Criteria for just which tumours are 'resectable' are still evolving; deciding whether or not residual tumour after chemotherapy is actually viable remains difficult as does the management of the patient

who undergoes a complete response. The role of hepatic artery infusion of cytotoxic agents for down-staging and systemic administration prior to resection of tumours for which there is no requirement for downstaging (ie in the neo-adjuvant setting, with a view to limiting subsequent recurrence and extrahepatic disease) are both areas of active research.

National Institute for Health and Clinical Excellence guidelines

The rapid pace of change in the field of chemotherapy for metastatic CRC brings its own problems. In setting up new clinical trials it is difficult to determine the appropriate control arm and it is difficult for agencies such as the National Institute for Health and Clinical Excellence (NICE) to respond in a timely manner. The current NICE guidelines suggest that, on the basis of clinical- and cost-effectiveness, either irinotecan or oxaliplatin, in combination with 5-FU/FA can be recommended for routine first-line therapy for advanced CRC. Irinotecan monotherapy is recommended in patients who have failed an established 5-FU-containing regimen and oxaliplatin with 5-FU/FA as subsequent therapy after failure of first-line irinotecan-based treatment.[20] NICE appraisal of the monoclonal antibodies has concluded, with some controversy, that neither bevacizumab nor cetuximab is recommended on the basis of cost-effectiveness.

Palliative therapy for hepatocellular carcinoma

Locoregional therapies including intratumoural injection of agents such as alcohol, radio frequency ablation or intra(hepatic) arterial approaches are widely used when surgical resection is not possible. These approaches, based on physical ablation of the tumours, are much more effective with small tumours (<5 cm). Indeed below this value there is increasing evidence that they approach the efficacy of surgical resection. The intra(hepatic) arterial approaches offer some degree of selectivity or tumor 'targeting'. TransArterial Chemo-Embolisation (TACE) tends to be used for larger tumours, and this includes the bulk of those who are diagnosed with symptoms (as opposed to through screening procedures).

TransArterial ChemoEmbolisation

The rationale for this approach is based on the dual blood supply to the liver, with the portal vein predominantly supplying normal hepatocytes and the hepatic artery largely supplying the tumour. Therapeutic tumour embolisation injecting various embolic materials, under fluoroscopic control, at the time of diagnostic hepatic arteriography into the tumour-feeding vessels has replaced surgical ligation of the hepatic artery. Although more than half the patients show clear evidence of tumour regression there is minimal impact on overall survival. Direct infusion of cytotoxic agents into the hepatic artery may allow an increase in drug exposure (the time/concentration interval) of the tumour up to 400-fold (depending on the properties of the drug employed). Again, response rates are significantly higher than for the same treatment administered systemically but survival benefit has not been demonstrated. When lipiodol, an oily contrast medium, is injected into the hepatic artery at the time of arteriography subsequent CT 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.

TACE attempts to enhance the effect of arterial embolisation, as described above, by the addition of intra-arterial chemotherapy. Typically, 60–75 mg of doxorubicin is 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. Effective embolisation is often associated with fever, pain and vomiting for up to five days which will spontaneously subsides. Although early prospective randomized trials again failed to confirm improvement in survival the drug levels achieved were up to 40 times higher than those in surrounding normal tissue and produced radiological response rates of up to 83%.[21] Two more recent randomised controlled trials and a meta-analysis[22,23] have reported a clear survival benefit for patients receiving TACE as opposed to those treated with best supportive care. In both cases, the survival rates were in the region of 20% better than the control arm. The main cause of death in both trials was tumour progression highlighting the fact that although TACE is an effective treatment, further improvements are required. The inclusion criteria for the latter studies were strict focusing on patients with minimal symptoms and very good liver function. Outside these strict criteria, superiority of TACE over systemic chemotherapy has not yet been demonstrated.

Systemic therapy for hepatocellular carcinoma

Response rates for single-agent chemotherapy are low and significant durable remission is rare. The most widely used single cytotoxic agent has been doxorubicin, an anthracycline. In systematic reviews of randomised trials of doxorubicin therapy, however, no significant survival effect was discernable. No other systemic therapies have fared significantly better and systemic therapy is now largely confined to clinical trials. Combination chemotherapy appears to give a higher response rate, though again the duration of remission is usually short. In general, even for well-selected patients, the expected objective response is only around 20–30% and, as such, seems unlikely to have a significant impact on survival. A phase II study of a four-drug systemic combination regimen (cisplatin, recombinant interferon alpha-2b, doxorubicin and 5-FU (PIAF)) was encouraging showing that although the response rate was not high (25%), 9 of the 13 partial responders had their disease rendered resectable.[24] A prospective randomised study comparing PIAF to conventional systemic doxorubicin, however, suggested that any benefit in terms of increased survival was counteracted by increased toxicity.[25]

An alternative systemic approach has been endocrine manipulation based on reports of oestrogen receptor expression in

some HCCs. Early small studies with anti-estrogenic and anti-androgenic agents showed some promise. Recent large-scale prospective controlled studies have, however, refuted any role for hormonal agents including tamoxifen.[26]

Neuroendocrine tumours metastatic to the liver

Neuroendocrine tumours (NETs) are derived from Kulchitsky cells, which are widely distributed in the body. Typically tumours are described as originating from fore-, mid-, or hindgut. A proportion of tumours are 'functional' with secretion of hormones that can manifest as clinical symptoms. The carcinoid syndrome of episodic flushing, increased stool frequency, abdominal pain, bronchial constriction and right-sided heart disease, caused by systemic action of vasoactive peptides (5-hydroxytryptamine, kinins and prostaglandins) secreted by the tumour, invariably indicates the presence of hepatic metastases, usually originating from a primary tumour of the small bowel. For such patients prolonged survival without active anti-cancer therapy remains a possibility with median five-year survival rates of around 38%. A minority of patients may present with solitary liver metastases or limited liver involvement and in this sub-group of patients surgical resection should be considered.[27] For the majority of patients with diffuse, unresectable disease other modalities of treatment such as embolisation/chemoembolisation, systemic chemotherapy and biological or hormonal agents need to be considered to palliate symptomatic hepatomegaly and hormonal symptoms.

Tumour embolisation/chemoembolisation

Selective embolisation of hypervascular carcinoid liver metastases is attractive as a palliative treatment option as it allows tumour debulking as well as reduction in the tumour's capacity for hormone secretion. Objective response rates of between 48–81% have recently been reported with symptomatic benefit in as many as 80% of patients.[28] It is common practice to repeat a series of embolisations over a period of time following an initial response. A retrospective series from the University of Texas M.D. Anderson Cancer Center reported a deleterious effect on response rates of chemoembolisation versus embolisation alone with a trend towards greater toxicity.[29]

Chemotherapy

Single-agent activity is poor with response rates of less than 10%. Combination studies have produced higher response rates and have centred on the use of streptozocin-based combinations. Evidence for improved survival from chemotherapy compared to supportive care is lacking. A study randomising patients with pancreatic islet cell tumours between the addition of 5-FU or doxorubicin to streptozocin-based therapy, however, indicated a significant increase in survival (2.2 *v* 1.5 years) in favour of the anthracycline-containing regimen.[30] The applicability of these results to other types of NET is not clear. Newer agents have failed to demonstrate superiority. There is a limited evidence base to support the treatment of metastatic carcinoid tumours with high proliferative indices using cisplatin and etoposide chemotherapy. One study reported response rates of 67% among a group of patients with prospectively identified high-grade tumours, although this effect remains to be validated by larger controlled studies.[31]

Hormonal treatment

Hormone secretion from functional NETs is mediated via stimulation of somatostatin receptors (SSTR) on the tumour cell membrane. The advent of synthetic somatostatin analogues, which can down-regulate this process, have revolutionised the management of the carcinoid syndrome. Dramatic improvement or complete disappearance of symptoms (flushing more so than diarrhoea) is experienced by the great majority of patients, with minimal toxicity. The first analogue (octreotide, Sandostatin®) was administered subcutaneously three times per day but slow release formulations are now available with similar activity and toxicity profile but with more convenience and these have now become the gold standard therapy. Sandostatin LAR® (20–30 mg every four weeks by deep intramuscular injection), or lanreotide (Somatuline® LA, 30 mg every two weeks by deep intramuscular injection) achieve similar response rates, but with increased compliance and patient satisfaction.

The extent to which these analogues exert an anti-proliferative effect remains controversial. Disease 'stabilisation' has been frequently reported and there are occasional reports of tumour shrinkage.[32] Thus, in the German Sandostatin Study, 52 patients with progressive disease were evaluated following treatment with short-acting octreotide with tumour stabilisation for at least three months seen in around one third of patients[33] and Eriksson *et al* demonstrated an 81% rate of disease stability among a cohort of 55 patients with advanced progressive neuroendocrine tumours.[34] However, the indolent course of these tumours makes disease stabilisation difficult to quantify as a true anti-proliferative effect of the drug. Nevertheless, there are retrospective cohort studies suggesting that since the introduction of octreotide there has been a striking increase in the survival of patients with carcinoid tumours but confirmation must await properly controlled clinical trials.

Interferon

Interferon (IFN) produces biochemical responses in up to 40% of patients with functional NET and radiological tumour shrinkage in up to 10%.[35] The mechanism of action is unclear but may be a direct inhibition of cell proliferation or immune-mediated cytotoxicity. *Faiss et al* randomised treatment among naive patients to either a somatostatin analogue alone, IFN alone or the combination. No significant differences in the rates of partial remission, stable disease or tumour progression were observed between the three groups, although a significant reduction in symptoms was seen in the combination group.[36] Interferon alpha remains a possible treatment option for the palliation of symptomatic hepatic metastatic carcinoid disease

but the evidence base fails to support a survival advantage and its toxicity can substantially impact on quality of life.

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