Hepatocellular Carcinoma: Systemic Therapy and Liver Transplantation - Two ends of the Therapeutic Spectrum

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and causes nearly 1 million deaths annually worldwide. The only curative treatment is surgical resection or liver transplantation but only a minority of patients is suitable for these interventions. Local ablative therapies such as ethanol injection and radiofrequency ablation can induce long-term survival in selected patients but the majority of patients are suitable only for palliative treatment because of the extent of their tumour or background liver disease or both. In selected patients Transarterial chemoembolisation (TACE) has been shown to improve survival but for those in whom TACE is not feasible, systemic therapy may be considered.

Clinical Trials of Systemic Chemotherapy for HCC

The patient group for whom radical curative or local treatments are not appropriate typically have a poor performance status, impaired renal function, ascites and thrombocytopenia, all of which reduce tolerance to chemotherapy reduce the chance of a good response. Furthermore their survival is frequently determined by the severity of their background liver disease rather than their cancer and in one report only 10% of deaths in HCC patients were classified as cancer related deaths.

Trials of Doxorubicin

Doxorubicin has come to be regarded by many as the standard chemotherapy drug for HCC. The initial report of a 79% response rate\(^1\) in Ugandan patients treated with doxorubicin was encouraging but no trial has subsequently achieved such impressive results. On the contrary the overall response rate for a response rate for 734 patients treated in 16 trials over the past 30 year is around 18%\(^2\) and in a recent large randomised trial using modern criteria the response rate was only 11%\(^3\). Remarkably, only one randomised controlled trial has compared doxorubicin with supportive care and this trial reported a survival of 10.6 weeks in the treated arm compared with 7.5 weeks in untreated controls. In summary the response rate for single agent doxorubicin is poor and there is no convincing evidence that it prolongs survival.

Combining other cytotoxic drugs with doxorubicin has also been explored and the initial report combining cisplatin, doxorubicin, fluorouracil and alpha-interferon (PIAF) yielded a promising response rate of 26%
appeared\(^5\). Although there were no complete radiological responses, nine patients who underwent surgical resection 4 had a pathological complete response. This confirms that HCC can be chemosensitive and that radiological objective response can also underestimate the true response. However a follow-up study including 145 patients had a lower rate of only 17\(^\%\)\(^7\) and a recent randomised trial demonstrated no significant difference in survival between single agent doxorubicin and the PLAF regimen\(^4\). Other combinations based on doxorubicin have been less impressive in phase II studies and have shown increased toxicity with no apparent benefit.

**Other Cytotoxic Agents**

Many other cytotoxic agents have been evaluated in HCC. Oral fluorouracil, gemcitabine, ifosfamide, paclitaxel, vindesine, raltitrexed, trimetrexate, mAMSA and irinotecan appear to be inactive and not worthy of further study. Cisplatin, etoposide, intravenous fluorouracil and topotecan have some activity although none are clearly superior to doxorubicin. Non-doxorubicin combinations have also been evaluated in phase II studies and, while most trials have been disappointing, the doublet of etoposide and epirubicin gave an encouraging response rate of 39\(^\%\) \(^8\) and a median overall survival of ten months, which is worthy of further study. There have been several randomised trials of combination therapies but none have demonstrated a significant survival benefit for any arm.

In summary, during the past 30 years since the initial report of doxorubicin little progress has been made and there remains widespread scepticism about the role of chemotherapy. No drug or combination has been shown to be superior to single agent doxorubicin which itself has not been convincingly shown to improve survival over supportive care. Furthermore no trial has systematically assessed clinical benefit or quality of life. On the basis of this it is reasonable to argue that there is no standard drug and that supportive care should be the control arm of any randomised trial. Clearly there is a need for well-designed randomised trials, which are adequately powered to address questions of survival, clinical benefit and quality of life in a well-characterised and homogeneous patient population.

There is also a need to refine our selection of patients so that those most likely to benefit are treated and those that are not are spared toxicity. This requires an understanding of the clinical prognostic factors, the mechanisms of tumour resistance and the development of predictive tests based on prospectively gathered molecular profiling or functional imaging.

**Non-chemotherapy Approaches for Systemic Therapy**

Randomised trials have confirmed that tamoxifen\(^9\)\(^,\)\(^10\) and octreotide\(^11\) are ineffective while evidence of any benefit for interferon and androgens is unconvincing. There is therefore and urgent need to explore novel agents and trials are currently underway evaluating antiangiogenics such as bevacizumab, receptor tyrosine kinase inhibitors and COX 2 inhibitors amongst others.

**Liver Transplantation**

Liver transplantation is a potentially curative treatment for HCC complicating cirrhosis if confined to the liver. Early results for transplantation were poor with high recurrence rates but the outcomes have improved dramatically with defined selection criteria. Most centres apply the Milan selection criteria which include solitary
tumours with diameter < 5cm, or if multifocal, less than 3 nodules, no more than 3cm diameter each. Vascular invasion on imaging and extrahepatic manifestations are considered contraindications to OLT. Applying these criteria achieves a 66% 5 year survival and 6-8% tumour recurrence rates which is similar to the results of transplantation for non-malignant disease (71% at 5 years)\textsuperscript{123}.

Resection Versus Transplantation

No randomised trials have compared resection with transplantation for single nodule HCC patients that appear to be both resectable and transplantable. Furthermore it is difficult to draw conclusions from historical comparisons since resected patients always have better liver function and the results for transplantation are heavily influenced by waiting list which can mean a drop out rate of 23% at 12 months\textsuperscript{13}. A short waiting time (mean 62 days) resulted in a 85% 2-year survival, whereas a longer waiting time (mean 162 days) resulted in a 23% ‘drop-out’ rate and <60% 2-year survival. Consequently some transplant centres have used a strategy of liver resection first and transplantation later for tumour recurrence or deterioration of liver function.

Adjuvant Therapy pre Transplantation

Pre-operative TACE has been used as a holding measure or down staging procedure before transplantation but there are no randomised trials exploring the efficacy of this technique in this setting.

Other Transplant Strategies

The long waiting times arising from limitation of donor availability means that up to 30% of HCC patients develop contraindications to cadaveric liver transplantation. Consequently alternative strategies have emerged including living donor liver transplantation (LDLT) and domino liver transplantation (DLT).

LDLT has been used in Japan for many years\textsuperscript{14} and still represents the principal type of LT in this country. For most adults, right-lobe grafts are needed to provide sufficient hepatic mass and there is a donor mortality risk of 1%. Furthermore the ethics of live donor liver transplantation for HCC in which recurrent disease can occur in up to 20% needs to be considered and contrasted with a policy of increasing cadaveric organ donation.

In domino transplantation, the explanted liver of a patient with familial amyloidotic polyneuropathy (FAP) is donated to another patient\textsuperscript{15}. There is however a risk of the recipient developing symptoms of FAP and in the context of HCC, it should be offered to cirrhotics with advanced, non-transplantable malignant disease.

Conclusion

In a cirrhotic patient with any degree of liver dysfunction, solitary tumours with diameter <5cm or if multifocal HCC, less than 3 nodules no more than 3cm each, can be considered for liver transplantation. These criteria are being revisited with better and standardised protocols of imaging, but need to take into account the waiting time. For the vast majority of patients transplantation will not be appropriate and palliative therapy is needed. The currently available evidence suggests that systemic chemotherapy therapy is minimally effective and poorly tolerated but the majority of trials are small and patient groups heterogeneous. Careful patient selection and properly powered clinical trials will be required to convincingly demonstrate the value of such treatment. Meanwhile novel agents are being evaluated and the results of these trials are eagerly awaited.
References


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American Society of Clinical Oncology
British Oncology Association
The Royal Society of Medicine
EORTC GITCG
UK NETwork
Grant Reviews

MRC: Referee for Clinical Research Training Fellowships
CRIUK-Deputy Key Clinician Member of New Agents Committee

Manuscript Peer Review

European Journal of Cancer
British Journal of Cancer
Lancet
Clinical Cancer Research

Invited Talks

Nov 2003  Anti-cancer agents. MRES course Institute of Child Health
Nov 2003  Anti-cancer agents. BODMA regional meeting. MRC clinical Trials Centre
Jan 2004  Surveillance for Patients at high risk of Gastric Cancer. Medical and Surgical
          Master Class, Royal Free Hospital
March 2004 New agents in colorectal cancerDept of Surgery Royal Free Hospital
June 2004  Hepatocellular Carcinoma St Marys Hospital
July 2004  Hepatocellular CarcinomaThe Royal London Hospital
Oct 2004  Systemic treatment for Hepatocellular Cancer. Hepatocellular carcinoma screening
diagnosis and management, Royal Free Hospital
Dec 2004  Hepatocellular carcinoma: defining effective intervention Royal College of
          Physicians . Key advances in the Effective management of Upper GI malignancy
Jan 2005  Recent advances in the systemic treatment of colorectal cancer. The colon
          Masterclass Royal Free Hospital