Current management of liver cancer

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Epidemiological relevance of liver cancer

Hepatocellular carcinoma (HCC) is a major health problem [1] being the fifth most common cancer worldwide with 626,000 new cases in 2002 [2]. The incidence of HCC is increasing in Europe and the United States [3], and is currently the leading cause of death amongst cirrhotic patients [1]. Worldwide, HCC is the third cause of cancer-related death, behind only lung and colon cancers [2]. HCC usually develops in the context of inflammation and organ injury: it coexists with cirrhosis in more than 80% of the cases. Several underlying etiologies, most common infections and toxics, can cause cirrhosis. Hepatitis B virus (HBV) infection is the main risk factor for HCC in Eastern Asia and Africa [1]. Aflatoxin B exposure has a synergistic effect with HBV infection in the development of HCC. In Western countries and Japan, HCV infection is the main risk factor. Approximately 20% of all the individuals infected with HCV worldwide will develop cirrhosis, and among these, 3–5% will develop HCC every year. Surveillance with ultrasonography every 6 months in cirrhotic patients is recommended [4,5].

Management of liver cancer

There is agreement in a common classification for HCC endorsed by European and American scientific societies that links tumour stage with treatment startegy [1,4,5]. According to this classification, around 30–40% of HCC patients are eligible for potential curative treatment (resection, transplantation or local ablation) [1] at the time of presentation in the West (early stages), whereas the remaining are considered for chemoembolisation [6,7] (intermediate stages: ~20%) or sorafenib [8] (advanced stages and progressions from previous stages: ~40%), as a result of positive data in recent randomised studies. The strength of evidence in the management of HCC has been classified according to the recommendations of the National Cancer Institute, where a hierarchy is established considering the strength of study design and the strength of endpoints [9] (Table 1).

Table 1
Levels of evidence in the management of HCC[a]

Treatments assessed	Benefit	Evidence
Surgical treatments		
Resection	Increased survival	3iiA
Adjuvant therapies	Uncertain	1iiA
Liver transplantation	Increased survival	3iiA
Neo-adjuvant therapies	Treatment response	2iiDiii
Loco-regional treatments		
Local ablation	Increased survival	3iiA
Radiofrequency ablation	Better local control	1iiD
Chemoembolisation	Increased survival	1iiA
Internal radiation (^{131}I, ^{90}Y)	Treatment response	3iiDiii
Arterial chemotherapy	Treatment response	3iiDiii
Systemic treatments		
Sorafenib	Increased survival	1iA
Systemic chemotherapy	No benefit	1iiA
Tamoxifen	No benefit	1iA
Interferon	No benefit	1iiA

[a] Classification of evidence adapted from NCI: www.cancer.gov [9].
Study design:
Randomised controlled trial, meta-analysis = 1
(Double-blinded: 1i, non-blinded: 1ii).
Non-randomised controlled trials = 2.
Case series = 3 (Population-based 3i, non-population based, consecutive 3ii, non-population based, non consecutive: 3iii).
End-point:
Survival (A), Cause-specific mortality (B),
Quality of life (C), Indirect surrogates (D).
Disease free survival (Di), progression-free survival (Dii), tumour response (Diii).

Resection and liver transplantation

Resection and liver transplantation (LT) achieve the best outcomes in well-selected candidates, and

compete as the first option in patients with early tumours from an intention-to-treat perspective [10,11]. Resection yields good results (5-year survival 60–70%) in candidates who present with single tumours and excellent liver functional reserve (3iiA). Japanese authors use the indocyanine green clearance to identify the best candidates [12], whilst portal pressure and bilirubin are the parameters used in Europe [11]. Tumour recurrence complicates 70% of cases at 5 years, and no adjuvant therapy has unquestionably proven to prevent this complication through RCTs [10–12] (1iiDiii).

Liver transplantation is the first choice for patients with small multinodular tumours (three nodules $\leqslant$3 cm) or those with advanced liver dysfunction [11,13] (3iiA), since it may simultaneously cure the tumour and the underlying cirrhosis. Patients with single HCC $\leqslant$ 5 cm or up to 3 nodules $\leqslant$3 cm are the best candidates for LT, and achieve 70% survival at 5-years with a recurrence rate below 15% [11,13]. The major drawback of LT is the scarcity of donors. Although adjuvant therapies, whilst on the waiting list, are used in most centres to prevent tumour progression, their impact of these treatments on recurrence and survival is unknown (3iiDiii).

Local ablation

Percutaneous ablation with percutaneous ethanol injection (PEI) or radiofrequency ablation (RF) achieves complete responses in more than 80% of tumours smaller than 3 cm in diameter and provide 5-year survival rates of 40–70% [1,14,15]. The best outcomes have been reported in Child–Pugh A patients with small single tumours, commonly less than 2 cm in diameter [15]. Treatment of patients with larger tumours (3–5 cm), multiple tumours (three nodules <3 cm) and advanced liver failure (Child–Pugh B) is reasonable on individual bases (3iiA).

Four recent RCTs comparing radiofrequency ablation versus PEI in early tumours showed a significant benefit favouring RF in terms of local control of the disease compared with PEI (2 year local recurrence rate: 2–18% versus 11–45%) [16], (1iiD). However, the data did not provide enough evidence to support survival benefits coming from RF, and further research is needed (1ii A).

Chemoembolisation and other local treatments

Arterial embolisation is the most widely used primary treatment for unresectable HCC RF [1]. Obstruction of hepatic artery induces extensive necrosis in large vascularised HCC. Embolisation agents – usually gelatin or microspheres – may be administered together with selective intra-arterial chemotherapy mixed with lipiodol (chemoembolisation). Doxorubicin, mitomycin and cisplatin are the commonly used anti-tumoural drugs [7]. Arterial embolisation achieves partial responses in 15–55% of patients [7], and significantly delays tumour progression and vascular invasion [6] (1iiDii).

Survival benefits of chemoembolisation have been reported in two studies [6,17], one of which identifies treatment response as an independent predictor of survival. Meta-analysis showed a beneficial survival effect of embolisation/chemoembolisation in comparison to the control group (1iiA) [7]. Survival benefits were not identified with embolisation alone, but the number of individuals analysed is still low. There is no good evidence for the best chemotherapeutical agent (doxorubinin or cisplatinum) and the optimal retreatment strategy (1iiA).

None of the other loco-regional therapies have resulted in a proven advantage in terms of survival. Some strategies provide objective response rates above 20%, as in the case of internal radiation with 131-I-labelled Lipiodol or Y-90, or arterial lipiodolisation [16]. These treatments deserve further analysis in the setting of phase III investigations.

Systemic therapies: Sorafenib

Systemic therapies such as standard chemotherapeutic agents do not have significant efficacy in HCC [1,7]. Systemic chemotherapy has been assessed in more than 20 RCTs with negative survival results [7]. Response rates of around 10% can be achieved with doxorubicin and cisplatinum, but are associated with severe complications in cirrhotic patients. Similarly, several RCTs and meta-analysis of pooled data showed negative outcomes for patients with advanced tumours treated with tamoxifen. This was also the case with anti-androgen agents and immunomodulatory therapies, such as interferon. Therefore, until recently there was no first line treatment option for advanced tumours and this represented an unmet need. In fact, western regulatory agencies have not approved any systemic tretament for HCC so far, a unique case among solid tumours.

Recently, the phase III clinical trial assessing sorafenib, a multikinase inhibitor blocking VEGFR, Raf, PDGFR among other kinases, conducted in 602 patients with advanced measurable HCC was stopped at the interim analysis because survival advantages from sorafenib ($n = 299$) versus placebo ($n = 303$) [8]. Based on 321 deaths, the hazard ratio for death was

0.69 (95% CI: 0.55–0.86; $P = 0.0005$), representing a 44% improvement in survival (median survival for sorafenib arm 10.6 months versus 7.9 months for placebo (1iA). The study showed a significant benefit in terms of time to progression (TTP) assessed by independent radiological review with a median TTP of 5.5 months for sorafenib and 2.8 months for placebo. Sorafenib was well tolerated and is the first agent to demonstrate a statistically significant improvement in survival for patients with advanced HCC. This effect is clinically meaningful and establishes sorafenib as the first-line treatment for these patients after 30 years of research and more than 100 conducted RCTs.

Conflict of interest statement

Josep M Llovet, MD is a medical advisor for Bayer Pharmaceuticals, Biocompatibles and MDS Nordion.

Acknowledgement

Grant support: Josep M. Llovet is Professor of Research – Institut Català de Recerca Avançada (ICREA, Generalitat de Catalunya).

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