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Medical treatments for hepatocellular carcinoma (HCC): what's next?

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introduction

Hepatocellular carcinomas (HCC) is the fifth most common malignancy worldwide. HCC incidence has doubled over the last 20 years in Europe [1]. This is probably related both to the improvement of life expectancy in cirrhotic patients and the increased incidence of cirrhosis due to viral hepatitis C. HCC incidence greatly varies across Europe from 14/100 000 men/year in Italy to 1.7/100 000 men/year in the Netherlands for males and 4/100 000 women/year in Spain to 0.3/100 000 women/year in Ireland for females. In 2005 it is projected that there will be 667 000 new patients with HCC worldwide [2].

In 60% to 90% of patients, HCC is due to liver cirrhosis secondary to alcohol, hepatitis C or B. In the case of cirrhosis, the annual incidence of HCC is about 4% [3]. However, despite the available treatment options, the incidence still nearly equals the mortality rate and more than 80% of patients present with advanced disease. Moreover, for the patients who undergo orthotopic liver transplantation (OLT), surgical or non-surgical ablation, the recurrence rate may be as high as 50% at 2 years [4, 5]. The ability to conduct large clinical trials in patients with HCC has been mainly hampered by the severe co-morbidities of cirrhosis, the advanced nature of the disease at presentation, the heterogeneity of daily clinical practice for these patients between centers and the distribution of patients primarily in developing countries where clinical research may be difficult to organize. There is an urgent need for new active and well-tolerated treatments to improve survival among patients with advanced HCC (palliative setting) and to increase long lasting remission after curative treatments (adjuvant setting). Treatment options for HCC in 2006 and the best settings to develop innovative therapeutic approaches are summarized in Figure 1. The active development of innovative therapeutic approaches and molecularly targeted agents in other malignancies offers the opportunity to study these agents in HCC and gives new hope for the future.

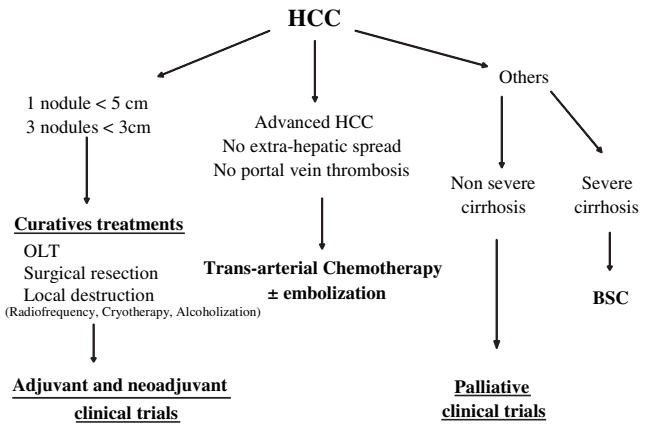
curative treatment for HCC

The management of HCC patients depends mainly on (i) the extent and location of the tumor and (ii) the underlying liver disease. In the case of HCC, the presence of cirrhosis, which is directly linked to the patient's life expectancy and the tolerance of the possible treatments, influences the choice of the therapeutic strategy. This also explains some disparity between the results reported in Asiatic patients suffering mainly from viral cirrhosis and European patients, usually older and suffering mainly from alcoholic cirrhosis. Treatments may be curative or palliative according to the HCC extension and the severity of the underlying liver disease. There are only few randomized trials with curative treatments and, therefore, a low level of evidence and great disparity in the recommendations and practices among centers and countries [6].

Three curative methods are currently available: OLT, surgical resection and local destruction (LD). In the absence of a randomized trial, OLT is considered as the most efficient HCC treatment because the tumor, the cirrhosis and preneoplasic lesions are treated at the same time [7]. However, OLT using the Milan criteria (unique HCC ≤5 cm or three nodules of ≤3 cm maximum) is only applicable in 5%–15% of the cases because of its numerous contraindications and the lack of donor organs that increase the delay before OLT, with the risk of tumor progression and/or decompensation of cirrhosis [8]. When OLT is performed, long-term survival is about 60% in most series. In patients treated with LD or surgical resection the prognosis is rather poor because the recurrence rate in the liver is high and death related to cirrhosis is frequent [8, 9]. Surgical resection may be discussed in cases of small HCC in a healthy liver or Child-Pugh A cirrhosis [9]. In such patients survival rates can be as high as 70% at 5 years [3]. However, larger HCC may be resected with good results in well differentiated and slow growing tumors [10]. Local destruction (LD) of HCC is the most recent curative treatment developed. LD may be done using chemical destruction (alcohol or acetic acid) or physical destruction by thermal ablation (cryotherapy, radiofrequency). These methods are simple (short hospitalization) and well tolerated in the absence of deleterious effect in cirrhotic livers and may be done by a percutaneous approach guided by ultrasound or computer tomography (CT) scan.

Thermal ablation gives a more homogeneous and larger necrosis and has replaced ethanol injection in many centers. Main indications are small lesions developed in Child-Pugh A or B cirrhosis.

LD results in a complete destruction in 90% of small lesion (≤3 cm) [11]. LD is not feasible in cases of ascites, hypocoagulation, subcapsular HCC locations, which increase the risk of hemorrhage and tumor dissemination and make it impossible to locate the tumor properly. Thermal ablation is



OLT:orthoptic liver transplatation:BSC:best supportive care

Figure 1. Treatment options for hepatocellular carcinoma in 2006.

also contraindicated in HCC located close to the hilar region, extrahepatic organs, diaphragm or large vessels [11].

Overall retrospective comparison of thermal ablation and alcoholization has suggested that the two methods give similar results. However, radiofrequency requires less treatment sessions than alcoholization and seems more active in one recently published randomized trial in terms of 2-year disease-free survival (96% versus 62%, $P = 0.02$) [12]. Finally, in six retrospective studies (912 patients) there were no differences between surgical resection and percutaneous ethanol injection in relapse-free survival [13].

adjuvant and neo-adjuvant treatment

Secondary HCC prevention after (or before) successful therapeutic interventions needs to be improved in order to make an impact on long-term survival of these patients. Many adjuvant treatments have been evaluated but mainly in small studies and almost never confirmed if positive.

Trans-arterial chemo-embolization (TACE) has been evaluated in patients with HCC waiting for an OLT in different studies. Most of them suggested a potential benefit for TACE in this specific subset of patients but they were not controlled [14]. In two studies, chemo-embolization treated patients were compared with historical controls from the same center. The results showed no benefit of TACE [15, 16]. Finally, a recent case–control study on almost 500 French patients concluded that with a mean waiting period of 4.2 months observed and 1.7 TACE procedure, pre-transplantation TACE does not influence post-transplantation overall and disease-free survivals [17]. Concerning chemotherapy before or after successful surgical resection, a meta-analysis has evaluated four therapeutic modalities: pre-operative transarterial chemotherapy, post-operative transarterial chemotherapy, systemic chemotherapy and a combination of systemic and transarterial chemotherapy. The authors concluded that only post-operative transarterial chemotherapy seems to improve survival and to decrease the cumulative probability of no recurrence, and that new randomized controlled trials evaluating this modality are thus required [18]. A randomized controlled trial comparing transarterial chemotherapy, systemic chemotherapy using the gemcitabine-oxaliplatin (GEMOX) regimen and no adjuvant treatment in 300 patients will start before summer 2006 in France.

Many other therapeutic approaches have been tested in the adjuvant setting. Muto et al. [19] have tested acyclic retinoid polyprenoic acid following either treatment of primary HCC with surgical resection or ethanol injection. Eighty-nine patients were enrolled in the trial. After a median follow-up of 38 months, recurrence rates were 27% in the treatment group and 49% in the placebo group [19]. Toxicity was mild with only increased nausea and headache in treated patients. This treatment is currently evaluated in a phase II/III trial in HCC patients with hepatitis C virus (HCV) in Japan.

Although it seems logical to give anti-viral treatments in HCC patients with chronic HCV infection because HCV eradication is an obvious therapeutic goal, the role of interferon (IFN) in decreasing the risk of HCC recurrences in curatively treated patients is still a matter of debate [20, 21]. Four randomized trials on 20–74 patients infected with hepatitis C virus on adjuvant IFN after successful treatment of HCC by surgical resection or LD have been performed [22–25]. Patients were assigned to intramuscular interferon alpha or beta, which was given daily (6 MIU) two to three times a week, followed by less frequent administration for 1–3 years. Therapy was discontinued in 10%–30% of the patients due to side-effects. All these trials showed decreased recurrence rates in patients treated with IFN, but only one of them had a benefit in long-term overall survival [24]. This treatment is thus potentially promising in HCV-related HCC patients (less than 20% of all HCC patients in Western countries), but long-term results on survival and confirmatory trials are still needed.

Immunotherapy for cancer is attractive because of the exquisite specificity of the immune response. Induction of an HCC-specific immune response can be accomplished, for example, by strategies targeting tumor-associated self-antigens or by adoptive transfer of immune effectors expanded and activated *ex vivo*. Two randomized trials have evaluated immunotherapy in HCC patients after curative resection. A first promising trial enrolled 150 patients who were assigned to adoptive immunotherapy or no adjuvant treatment. Autologous lymphocytes activated *in vitro* with recombinant interleukin-2 and anti-CD3 were infused five times during the first 6 months. The immunotherapy group had significantly longer recurrence-free survival and disease-specific survival than the control group. Overall survival did not differ significantly between groups in this study [26]. More recently, Kuang et al. [27] conducted a phase II randomized trial to determine whether autologous formalin-fixed tumor vaccine protects against post-surgical recurrence of HCC. Forty-one patients with HCC who had undergone curative resection were randomly allocated to vaccine treatment or control. Three intradermal vaccinations were administered at 2-week intervals starting 4–6 weeks after surgery. Vaccination significantly prolonged the time to first recurrence and improved recurrence-free survival and overall survival rates [27]. In both trials the tolerability of the immune treatment was excellent.

Intra-arterial radioactive lipiodol [28] resulted in encouraging results in one randomized trial. Forty-three

patients who underwent curative resection for HCC and recovered within 6 weeks were randomly assigned one 1850 MBq dose of ^{131}I-lipiodol or no further treatment. An interim analysis showed a significant increase in disease-free survival in the treatment group compared with the controls, without significant ^{131}I-lipiodol-related toxic effects. A new randomized controlled trial with ^{131}I-lipiodol in this setting is currently ongoing in a larger population.

Although many therapeutic approaches seem promising in the adjuvant treatment of HCC after surgery or LD, the results observed in these trials have to be confirmed in larger randomized controlled studies demonstrating a clear survival benefit before secondary prevention with one of these strategies should enter clinical practice.

palliative treatment

Palliative treatments for HCC are indicated if there is no curative treatment option and four palliative treatments will be described.

transarterial chemo-embolization (TACE)

TACE is performed through hepatic arteries using a mixture of lipiodol and antineoplastic drugs combined with an arterial embolization. From 1990 TACE has been extensively studied and gives a 30% overall response rate and a post-embolization syndrome with pain, fever and elevation of hepatic enzymes is frequent. Aggravation of liver insufficiency related to ischemia of cirrhotic liver is the main risk and it may explain that in the 1990s three randomized trials failed to demonstrate a survival advantage [29–31]. TACE in a highly selected population of patients without liver insufficiency is efficient as demonstrated by two positive trials, reported in 2002, which reported an increase of overall survival after TACE (Table 1) [32, 33]. These trials have recently been confirmed by two meta-analyses [34, 35]. TACE is an active palliative treatment, which may be offered to patients who cannot benefit from curative treatment but who have still a good liver function (Child-Pugh A), are asymptomatic, have a good performance status (World Health Organization (WHO) grade <3), without portal hypertension or portal thrombosis, without renal insufficiency or extra-hepatic metastasis. Altogether, TACE is indicated in approximately 10% of the patients. After TACE in such selected patients the 2- and 3-year survival can be as high as 50%. The presence of a solitary nodule, hypervascularized HCC and high retention of lipiodol inside the HCC after TACE seem to be the best prognostic factors.

Table 1. Hepatocellular carcinoma: treatment by chemoembolization: recent randomized trials

	Lo et al. [24]	Llovet et al. [25]
Number of patients	79	112
Mean age (years)	62	65
HCC in viral cirrhosis	80%	90%
Okuda Stage I	47%	65%
Performance status WHO grade 0	43%	80%
Survival at 2 years		
Chemoembolization	31%	63%
Symptomatic treatment	11%	27%
Embolization alone	–	50%
P	0.005	0.009[a]

[a]Significant difference in favor of chemo-embolization.

systemic chemotherapy

Systemic chemotherapy has given disappointing results in inoperable HCC, possibly owing to the strong multidrug resistance gene (MDR) expression usually observed in this tumor [36, 37]. Furthermore, cirrhosis may reduce the capacity of the liver to metabolize and excrete cytotoxic agents and thereby augment toxicity. Finally, specific problems may occur when systemic chemotherapy is used in these patients with a cirrhotic liver and often viral infection. Clinicians have to pay a particular attention to platelet count and hepatitis B virus (HBV) status before initiating chemotherapy. In fact, liver cirrhosis that leads to portal hypertension may result in hypersplenism with platelet sequestration and thrombocytopenia leading to delayed treatment cycles, decreased chemotherapy dose-intensity and impaired treatment efficacy. Immunosuppressive chemotherapy can also reactivate chronic HBV infection further complicating medical management of the patient. In HbsAg-positive patients the instauration of an anti-HBV treatment such as lamivudine that is efficient with almost no side-effects, is strongly encouraged.

Among single-agent chemotherapy, adriamycin has long been considered as the reference drug, although it has demonstrated a very limited efficacy [response rate (RR) 0–29%] and no clinically relevant survival benefit (median 4 months). Even if in a randomized trial there was a small (absolute benefit of 3 weeks), but significant difference in overall survival (OS) when compared with best supportive care (BSC), tolerability was poor with a 25% toxic death rate [38]. Two meta-analyses have confirmed the lack of efficacy of adriamycin, which may impair the quality of life of HCC patients. Other classical drugs such as 5-fluorouracil (5FU) (RR 0%–10%), cisplatin (RR % –17%) and etoposide (RR 18%) are even less active [39, 40].

Polychemotherapy regimens combining these drugs are also poorly active with a RR between 15% and 20% for the combination of cisplatin, adriamycin, 5-FU and INF (PIAF) and the etoposide, cisplatin and 5-FU (ECF) regimen [41].

Phase II studies of new cytotoxic agents such as irinotecan, topotecan, paclitaxel and raltitrexed have also given disappointing results [42–44].

More recently, the GEMOX regimen (combining gemcitabine and oxaliplatin) has been evaluated with promising results in a pilot study and in a subsequent phase II trial [45, 46]. The response rates observed ranged from 17% to 40%, the disease control rate from 67% to 77% and the progression-free and overall survivals from 6 to 8 months and 9 to 13 months, respectively.

In conclusion, the overall disappointing results of systemic chemotherapy in advanced HCC patients support the research for other more active and specific treatments to be administered alone or in combination with systemic chemotherapy.

interferon

Interferon (IFN) has demonstrated some efficacy in the prevention of HCC development in patients infected with hepatitis B or C virus, even at the stage of cirrhosis. However, it has only a minimal efficacy in HCC with a marginal increase in overall survival, not clinically relevant, in one randomized trial (median survival 14.5 versus 7.5 weeks) in comparison to best supportive care [47] and no benefit at all in a second one [48]. In combination with chemotherapy, IFN seems to increase tumor response rate but does not improve survival [41].

hormonotherapy

Hormonotherapy has been used because several hormonal receptors have been described at the HCC tumor cells surface.

Anti-androgens have no demonstrated efficacy even combined with a luteinizing hormone releasing hormone (LHRH) agonist as well as flutamine and triptorelin [49].

Anti-estrogens have been discussed for a long time, but are now clearly inefficient in this disease as shown by several randomized controlled trials [50–52].

Somatostatin analogs (SA) inhibit cell proliferation by stimulation of somatostatin receptor subtypes (SRS) and it has been recently reported that SRSs were not expressed at the same level in HCC; SRS R1, R2, R3, R4 and R5 expression being observed in 46%, 41%, 64%, 0 and 75%, respectively, of HCC without relation with HCC stage and differentiation [53]. Since 10 years long-acting SA (LASA) have been used as palliative treatment for advanced HCC and in 1998 a small positive randomized trial was reported in favor of the use of LASA [54]. Since 2002, three larger randomized trials, on 70–270 patients, have tested LASA but failed to confirm any survival advantage [55, 56]. In conclusion, although occasional patients appear to have stable disease on LASA, overall the beneficial response in terms of time to tumor progression and survival seems limited.

what's next?

targeted therapies

anti-epidermal growth factor receptor (EGFR) therapies. Hepatocytes have the capacity for regeneration when the liver is damaged. In such a setting many growth factors including epidermal growth factor (EGF) and transforming growth factor alpha (TGFα), both ligand for EGFR are involved in liver regeneration. The expression of EGFR has been described in many HCC cell lines and in murine and human liver cells. EGFR mRNA is increased in some chronic liver diseases and in HCC [57]. Transgenic mice that overexpress TGFα in the liver show a high incidence of hepatoma suggesting the role of this pathway in hepatic carcinogenesis. Thus anti-EGFR therapies should be of great interest in patients with HCC. Recently, EGFR inhibiting agents such as the tyrosine kinase inhibitors erlotinib and gefitinib, have been approved for treatment of lung cancer, and cetuximab, a monoclonal antibody, has been approved for treatment of advanced colorectal cancer after irinotecan failure. Gefitinib has been shown to inhibit cell proliferation and metastatic spread in HCC cell lines and *in vivo* mice models, respectively [58].

Two phase II trials have recently evaluated erlotinib in patients with advanced HCC. Results showed an acceptable tolerance profile and some clinical activity with 35% and 25% progression-free survival at 4 and 6 months, respectively [59].

Cetuximab monotherapy has very recently been tested in the same setting with a good safety profile [60] but poor response rates and survival. Altogether there is a strong rationale to test anti-EGFR therapies in HCC patients but the results of the first clinical trials suggest that they shall not be so efficient when used as single treatment modality. New trial designs evaluating such agents in combination with chemotherapeutic regimens or with other biotherapies should be performed. The combination of the GEMOX regimen together with cetuximab is currently under investigation.

anti-vascular epidermal growth factor (VEGF) therapies. Angiogenic factors such as VEGF participate in the neovascularization of HCC [61–63]. VEGF is involved in both initial stages of development and after the tumor became established in mice models [63]. Also, VEGF has been shown to be increased in the plasma of HCC patients and to correlate with disease stage [64]. These data support the study of anti-VEGF agents in HCC treatment. The monoclonal antibody bevacizumab in combination with 5-FU-based chemotherapy is approved in the treatment of metastatic colorectal cancer patients and is available for phase I/II trials in other cancers. Preliminary data have shown that bevacizumab can be administered safely in carefully selected HCC patients and has shown modest clinical efficacy [65]. Its use in combination with the GEMOX regimen has been tested in 27 patients with advanced disease [66]. The combination therapy can be safely given but the response rates reported were comparable to those observed with GEMOX alone. Long-term survival will be presented soon and data should be carefully examined to determine if such a combination therapy seems promising. Finally, sorafenib, a novel inhibitor of VEGF receptor signal transduction and raf kinase, has shown some clinical activity in HCC and is currently evaluated in a large phase III randomized trial versus placebo.

other targeted therapies. Aberrant expression of both cyclin-dependent kinase and their inhibitors together with inhibitors of the cell cycle progression such as $p57^{KIP2}$ are important in the development of HCC [67, 68]. Thus, targeting the cell cycle appears to be a realistic strategy in HCC patients. Bortezomib, a dipeptide boronic acid that binds to the active site of the 26S proteasome and inhibits NFkB and flavopiridol that blocks cell cycle progression are the two molecules that have been currently clinically tested in this population [69, 70]. A phase I/II study recently indicated that bortezomib is well tolerated and may result in disease stabilization in HCC patients. Flavopiridol has been tested in association with irinotecan in a phase I trial. Disease stabilization was observed in several patients [69]. Further studies with these agents are currently ongoing.

Farnesyl transferase inhibitors, matrix metalloprotease inhibitors and antisense agents are also studied in the treatment of HCC but results are awaited.

immunotherapy

Some preclinical data strongly support the use of immunotherapy in HCC [71, 72]. Many trials evaluating active or passive immunotherapeutic regimen have been performed in patients with advanced HCC. Even if specific active immunotherapy or adoptive transfer of effector cells did give promising results in the adjuvant setting, these strategies do not seem efficient in patients with advanced disease [71, 72]. However, the recent advances in this field, including modulation of regulatory T-cell function [73] and the discovery of potent new drugable key cells involved in the innate antitumor immunity [74], may dramatically change the results of this type of treatment in the forthcoming years.

other therapies

Some evidence for the important role of cyclo-oxygenase 2 (COX2) in cirrhosis and hepatocarcinogenesis supported further investigations of the efficacy of COX2 inhibition in HCC patients [75, 76]. Inhibition of COX2 has been shown to reduce preneoplastic nodules and HCC in a dose-dependent manner in a mice model. However, the clinical development of COX2 inhibitors in such settings has been recently stopped because of their potential adverse effects on renal, hepatic and cardiovascular functions.

3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA redutase) inhibitors have cytostatic activity in cancer cells and a Japanese group has evaluated pravastatine in 83 consecutive patients with unresectable HCC. All patients were treated with trans-arterial embolization followed by oral 5-FU 200 mg/day for 2 months and were then randomly assigned to control ($n = 42$) or pravastatin 40 mg/day ($n = 41$) groups. Median survival was 18 months in the pravastatin group versus 9 months in controls ($P = 0.006$). The Cox proportional hazards model showed that pravastatin was a significant factor contributing to survival. New trials should be performed to confirm these promising results [77].

conclusions

Presently, in the absence of large randomized trials, the treatment strategies in HCC often remain a matter of center choice and 'philosophy'. To improve the management of these patients some guidelines should be implemented.

Firstly, these patients should be discussed by multidisciplinary staff involving at least hepatologists, surgeons and medical oncologists. Second, HCC extension, liver function and other co-morbidities (i.e. viral infection, alcoholism) have to be taken into consideration at the same time. Third, clinical trials in HCC have to be conducted according to the rules established by the consensus conference of Barcelona: randomized studies, including a great number of patients, using an intent to treat analysis, taking overall survival as a primary end point and the presence of a control group not receiving specific treatment [78].

Medical treatments are currently poorly effective in advanced HCC and their role after OLT, surgical resection or LD have to be explored. Identification of appropriate targets and effective targeted therapies in HCC represents a significant challenge and new hopes for the future. Although HCC is a heterogeneous disease (underlying hepatopathy, stage, genetic factors) and different pathways may be involved in hepatic carcinogenesis, advances in basic and translational research to improve our knowledge will lead to biologically-based clinical trials in the near future. On the other hand, some of the therapeutic approaches already tested in this disease have given some promising results and large confirmatory trials should be conducted before implementation in clinical practice.

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