

MINI-REVIEW

Advances in Management of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most frequent type of malignant liver tumor and a high impact health problem worldwide. The prevalence of HCC is particularly high in many Asian and African countries. Some HCC patients have no symptoms prior to diagnosis and many of them therefore present at late stage and have a grave prognosis. The well-established causes of HCC are chronic hepatitis B virus (HBV) or chronic hepatitis C virus (HCV) infection or alcoholic cirrhosis and nonalcoholic steatohepatitis. The Barcelona Clinic Liver Cancer (BCLC) Staging System remains the most widely used for HCC management guidelines. To date, the treatments for HCC are still very challenging for physicians due to limited resources in many parts of the world, but many options of management have been proposed, including hepatic resection, liver transplantation, ablative therapy, chemoembolization, sorafenib and best supportive care. This review article describes the current evidence-based management of HCC with focus on early to advance stages that impact on patient overall survival.

Keywords: Hepatocellular carcinoma - evidence base - clinical management - overall survival

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Introduction

Hepatocellular carcinoma (HCC) accounts for more than 90% of all malignant liver tumors, thus remaining a significant health problem worldwide especially in Asian and sub-Saharan African countries (Pourhoseingholi et al., 2010, Somboon et al., 2014; El-Serag, 2011, Wanich et al., 2016). HCC is also the sixth most common cancer, and the third global cancer related death (El-Serag, 2011). In Thailand, HCC is the most common cancer in men and the third most common cancer in women (Somboon et al., 2014). Most HCC occur in established background of chronic hepatitis B virus (HBV), chronic hepatitis C virus (HCV) infection or alcoholic cirrhosis (Chunlertrith et al., 2000, Wiangnon S et al., 2012, Liang et al., 2013). Nonalcoholic steatohepatitis (NASH), another important cause of cirrhosis, is also a growing problem globally (El-Serag, 2011). Importantly, several reports demonstrated that HCC could arise from non-cirrhotic NASH (Kawada et al., 2009; Mohamad et al., 2016).

A previous population-based study clearly showed that incidence of HCC is decreasing due to the implementation HBV vaccination program (Bruix and Sherman, 2011). However, HCC is long-known to be a fatal cancer, which most patients carry a grave prognosis (Somboon et al., 2014, Wanich et al., 2016). A large number of HCC patients present in intermediated to advanced stage, thus none of them could achieve curative therapy. The mean survival time after diagnosis in advanced stage HCC was reported to be as low as 10 months (Somboon et al., 2014).

To date, management of HCC is mainly based on the current standard staging system (Barcelona Clinic Liver Cancer: BCLC). The aim of the present article is to provide the current evidence-based practice review on treatment of HCC in early stage (curative therapy), intermediated stage (eg. transarterial chemoembolization: TACE), advanced stage and best supportive care in end stage of disease.

Hepatic Resection

Currently, liver resection is the first line curative treatment for single HCC with well-compensated Child A cirrhosis (Bruix and Sherman, 2011). These criteria were proposed in order to diminish the risk of postoperative liver decompensation, and improve long-term prognosis. Strict with these selection criteria, the perioperative mortality was reported to be less than 3% with a 5-year overall survival up to 70% (Lee et al., 2010).

Presence of portal hypertension (hepatic venous pressure gradient (HVPG) ≥ 10 mmHg) is considered as a relative contraindication for resection of HCC in cirrhotic patients. Several studies have shown that HVPG ≥ 10 mmHg was an independent predictor of liver failure and death in cirrhotic patients undergoing HCC resection (Bruix et al., 1996; Hidaka et al., 2012., Llovet et al., 1999). Of note, the 5-year survival after resection in cirrhotic patients with HCC and HVPG ≥ 10 mmHg and serum bilirubin ≥ 1 mg was 25%, compared with 74% in those with HVPG <10 mmHg and bilirubin <1 mg/dl (Llovet et al., 1999). A recent meta-analysis including 11

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studies reported HVPG ≥ 10 significantly increased risk of postoperative decompensation and death with pooled odd ratio of 3.04 and 2.07, respectively (Berzigotti et al., 2015). Other non-invasive tests have been studied to assess the presence of portal hypertension in these subsequent, for example detection of esophageal varices, platelet count less than 100,000 mm³, splenomegaly on imaging studies, or liver stiffness assessed by transient elastography >21 kPa (Roayaie et al., 2013; Kulik and Chokechanachaisakul, 2015; Llop et al., 2012). Model for End-stage Liver Disease >8 has been shown to predict poor outcome in HCC patients undergoing resection (Cucchetti et al., 2009). However, several studies have demonstrated an acceptable outcome in cirrhotic patients with clinical significant portal hypertension undergoing resection (Kawano et al., 2008; Ruzzenente et al., 2011). This finding has been attributed to an advancement in surgical technique for example laparoscopic approach and RFA-based resection device, together with limited liver resection, and improvement in perioperative care (Pai et al., 2008; Jarnagin et al., 2002; Poon et al., 2004). Therefore, HCC resection in compensated cirrhotic patients with significant portal hypertension is still a matter of debate.

The patients who undergo HCC resection are at high risk of tumor recurrence (nearly 70% at 5 years). Approximately 70% of recurrent cases occur within 2 years after resection, and are considered as local invasion or intrahepatic metastasis. Late recurrence (>2 years) is related with de novo tumor formation. The most powerful predictors of recurrence are presence of micro- and macrovascular invasion and multiple tumors (Llovet et al., 2005). Microvascular invasion presents in nearly 80% of patients with HCC diameter >5 cm. In patients with same Child-Pugh classification, postoperative 5-year recurrence and mortality rates were higher in patients with multiple than single lesions (75% and 42% vs. 60% and 32% in Child A, and 100% and 81% vs. 73% and 55% in Child B) (Ishizawa et al., 2008). Efforts have focused on the strategy for prevention of recurrent HCC after resection, and several molecular and genetic biomarkers have been studied as a predictor of late tumor recurrence (Nault et al., 2013). Studies evaluating neo-adjuvant or adjuvant therapies in decreasing HCC recurrence yielded unsatisfactory results therefore are not routinely recommended (Lau et al., 1999; Takayama et al., 2000). A randomized, double-blind, placebo controlled trial of sorafenib after resection or ablation to prevent HCC recurrence showed no benefit in recurrence-free survival (Bruix et al., 2015). So far, the most effective option is liver transplantation in those who are at high risk of postoperative recurrence.

The volume of future liver remnant (FLR) has been regard as a relevant prognostic marker after resection for HCC. FLR $<50\%$ in cirrhotic liver is associated with postoperative liver decompensation (Kubota et al., 1997). Ipsilateral portal vein embolization has been reported to increase the resectability of HCC in cirrhosis by diverting portal blood flow, thus resulting in hypertrophy of contralateral remnant lobe (Farges et al., 2003; Ribero et al., 2007). However, this method has not yet been

evaluated in randomized controlled trials.

According to the current AASLD guidelines, resection is recommended for treatment of single tumor in non-cirrhotic liver or well-compensated cirrhosis. In those with advanced liver disease, the benefit of resection should be weighed against the risk of postoperative complication. It should be taken into account that other treatment options might result in better long-term outcome in these patients.

Liver Transplantation

Liver transplantation (LT) is the ideal treatment for HCC because it eliminates the index tumor and cure underlying cirrhotic liver that serves as a risk of HCC development. However, the major limitation of LT is an organ shortage resulting in high dropout rate (12-25% per year) (Yao et al., 2002). The Milan criteria (1 lesion ≤ 5 cm, or up to 3 lesions with each ≤ 3 cm, no vascular invasion, and no metastasis) were firstly reported in 1996 by Mazzaferro and colleagues, and have been endorsed by the standard guidelines as criteria for patient selection. Applying these criteria for selection of LT candidate resulted in a 5-year overall survival of 75%, with perioperative mortality rate $<3\%$, and recurrence rate $<15\%$ (Mazzaferro, 2007; Mazzaferro et al., 1996). A systematic review published in 2011 showed that Milan criteria was the major prognostic determinant in HCC patients undergoing LT (Mazzaferro et al., 2011). In patients with HCC, applying the traditional MELD score for organ allocation is not practically suitable because these patients have almost preserved liver function when early HCC is firstly diagnosed. Therefore, the United Network of Organ Sharing (UNOS) assigns MELD exception points to HCC patients who are within the Milan Criteria starting at 22 points and increase 10% every 3 months as long as the tumor not exceeds the Milan criteria.

An expansion of the Milan criteria has been proposed by several research groups. The University of California San Francisco (UCSF) criteria (single tumor <6.5 cm, maximum of 3 total tumors with none >4.5 cm, and cumulative tumor size <8 cm) resulted in comparable 1-, 3- and 5-year survival after LT to Milan criteria (Toso et al., 2008; Earl et al., 2013). The "up-to-seven" criteria (the sum of the size of the largest tumor (in cm) and the number of tumors less than 7) were introduced in 2009 by the same group that firstly reported the Milan criteria (Farinati et al., 2009; Mazzaferro et al., 2009). However, applying the expanded criteria is offset by its negative impact on post-transplant outcome, and to non-HCC candidates who are also being on transplant list. Therefore, until further evidence becomes available, all the expanded criteria have not been widely accepted by standard international guidelines.

In patients with tumor burden beyond the Milan criteria, other treatments can be applied to downstage the tumor to meet acceptable criteria for LT. Trans-arterial chemoembolization (TACE) or radiofrequency ablation (RFA) are the common modalities used for downstaging (Bhoori and Mazzaferro, 2014). A prospective study reported that 70% of patients achieved successful downstaging, and 1-year and 4-year post-transplantation

survival rates were 96.2% and 92.1%, respectively (Yao et al., 2008). A systematic review including 8 studies and 720 patients who underwent LT after downstaging, reported a comparable 5-year survival rate with patients who initially presented within Milan criteria (Gordon et al., 2011). So far, firmly evidence-based consensus has not been made as studies were heterogeneous and most were uncontrolled observational in nature.

The primary aim of bridging therapy is to prevent tumor progression, thereby decrease risk of dropout from transplantation list. Most studies used TACE or local ablation with RFA or percutaneous ethanol injection (PEI) as a “bridge” until donor organ becomes available. Several observational studies have shown that applying this treatment while patients being on transplantation list were safe and associated with a decrease in dropout rate (De Luna et al., 2009; Chapman et al., 2008). Despite the lack of data from controlled clinical trials, it is generally recommended that bridging locoregional therapy is recommended if the waiting time is likely to be longer than 6 months (Bruix and Sherman, 2011; Clavien et al., 2012). Recently, living donor liver transplantation (LDLT) has been regarded as a potential strategy to decrease the dropout rate. It is reported that approximately 5 percent of all liver transplants performed in the United States are LDLTs. Several retrospective studies showed favorable outcome after LDLT in patients with HCC. An intention-to-treat analysis performed in 36 HCC patients who received LDLT demonstrated a significant lower dropout rate (0% vs 18.4%) and comparable 5-year overall survival (73% vs. 71%) with those received deceased-donor liver transplantation (DDLT) (Bhangui et al., 2011). A recent study from Japan including 197 HCC patients treated with LDLT showed an excellent long-term outcome with 5-year survival of 89.5% and recurrence-free survival of 97% (Yoshizumi et al., 2016).

Local Ablative Therapy

Local ablative therapy is considered the best option for patients with early HCC who are not suitable for resection or transplantation. The procedure can be done using either chemical: percutaneous alcohol injection (PEI), or thermal ablation: radiofrequency ablation (RFA) or microwave ablation. Multiple sessions may be required for complete ablation of the tumor.

Radiofrequency ablation (RFA)

Technically, procedure is performed by delivering a high frequency alternating current into the tumor through a needle electrode after intravenous sedation. An increase in temperature results in necrosis of the tumor. Complete response rates were reported to be 85% and 60% in HCC <3 cm and 3-5 cm, respectively (Livraghi et al., 2000; Yin et al., 2009). Interestingly, in patients with very early HCC (single tumor \leq 2 cm), 97.2% achieved complete tumor response with a major complication rate of 1.8% (Livraghi et al., 2008). Comparing efficacy between RFA and PEI, at least 3 meta-analyses have shown that RFA was superior to PEI in terms of local tumor control and overall survival (Cho et al., 2009; Orlando et al., 2009;

Weis et al., 2013). Whether RFA could replace resection in early HCC remains controversial. A meta-analysis of 1 randomized and 9 non-randomized controlled trials evaluating this issue showed that resection was superior to RFA in terms of overall survival (Zhou et al., 2010). However, survival in those with small HCC \leq 3 cm was comparable between two groups. Therefore, for ablating therapies, RFA has been increasingly favored over PEI as a curative therapy for early HCC unsuitable for surgical intervention. Most guidelines recommend that RFA should be considered for HCC number and diameter not exceed five and 5 cm, respectively. However, technical limitation of RFA can occur when the index tumor localizes closely to major blood vessel, diaphragmatic dome or liver edge.

Percutaneous alcohol injection (PEI)

Injection of ethanol induces coagulative necrosis of the tumor, as well as causing thrombosis of microvasculature. The best results were reported for PEI-treated patients with HCC diameter less than 2cm (Livraghi and Meloni, 2002). For tumor larger than 3 cm, PEI results in response rate of 50-60%, and local recurrence rate approximately 50%. Of note, overall survival after PEI is influenced by tumor size. The 5-year survival in Child A cirrhosis with HCC less than 2 cm after RFA was nearly 80%, compared to 39% in those with HCC 2-5 cm (Livraghi et al., 1992). Therefore, PEI is generally recommended to treat HCC less than 2 cm.

Other ablative therapies

Microwave ablation (MWA), in which the implanted electrode delivers a high frequency microwave into tumor tissue. The reported complete response rate after MWA was nearly 90%, with a 5- year survival of 51-57% (Dong et al., 2003; Lu et al., 2001). Two prospective studies showed that the efficacy of MWA and RFA was comparable (Lu et al., 2005; Ohmoto et al., 2009). However, this technique is still not widely available in routine practice

Transarterial Chemoembolization

Transarterial chemoembolization (TACE) is considered the first line therapy in patients with unresectable HCC in the intermediate stage of disease (BCLC stage B) (European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer, 2012). This method of treatment is appropriate in multifocal unresectable HCC without any vascular invasion or extrahepatic spread. The concept of therapy is based on that the blood supply for HCC is derived from hepatic artery than from portal vein. The benefits of this treatment are that the chemotherapy is directly administered to the tumor and the embolization eliminates tumor blood supply. Chemoembolization extends the median survival from 16 months to 19-20 months (Llovet and Bruix, 2003). The variation in improvement in survival depends on patient's baseline characteristics, tumor staging, liver function and general health status (Crissien and Frenette, 2014). There is no good evidence for the preferred choice of chemotherapeutic agents and the optimal time to repeat the procedure. Shortening

the duration between the procedures may lead to liver decompensation or liver failure. The use of drug-eluting microspheres to improve tumor exposure time and concentration of chemotherapeutic agent have reported a reduction in serious liver toxicity, and trend towards better tumor outcome compared to conventional TACE (Lammer et al., 2010).

Trans-arterial radioembolization consists of intra-arterial administration of microspheres loaded with radioactive compound, usually Yttrium-90. The procedure requires a multidisciplinary team approach. The macroaggregates albumin (MAA) scan must be done to predict the distribution of the microspheres and to exclude patients who have a hepato-pulmonary shunt >20% of the injected dose (Sacco et al., 2015). There is no randomized trial directly compare the survival in patients with intermediate-stage HCC. The retrospective data which compared TACE and radioembolization revealed longer median time to progression but no survival benefit for radioembolization (Sacco et al., 2011). It was found that radioembolization had less toxicity than TACE. Another advantage of radioembolization was that it could be done safely in patients who had concomitant main portal vein thrombosis which is a contraindication for TACE (Salem et al., 2010). Radioembolization requires sophisticated equipment and has a higher cost compare to TACE. However, the more favorable safety profile and less frequent treatments could translate into overall shorter hospital admissions.

Systemic Molecular Targeted Therapy

The current standard systemic treatment option for advanced HCC in patients with well-preserved liver function, and who are not a candidates for loco-regional therapy is Sorafenib (Bruix et al., 2011). Sorafenib, an oral multikinase inhibitor, is the first and only drug that has been demonstrated a survival benefit in advanced HCC. The landmark trial for Sorafenib was a multicenter double-blinded placebo-controlled study conducted in Western countries including 602 patients with advanced HCC and well-preserved liver function. At base line, 581/602 patients (97%) were in Child-Pugh class A. The study showed that Sorafenib improved overall survival and time to radiologic progression compared to placebo. The median overall survival was 10.7 months in the Sorafenib group compared to 7.9 months in the placebo group (HR 0.69; 95%CI 0.55-0.87; $p < 0.001$) (Llovet et al., 2008). The median time to radiologic progression was 5.5 months compared to 2.8 months in the placebo group ($p < 0.001$). The subsequent study which conducted in the Asian-Pacific region had a comparable design (Cheng et al., 2009). Also the majority (97%) of the patients in this study were in Child-Pugh class. Median overall survival was 6.5 months in the Sorafenib group compared to 4.2 months in the placebo group (HR 0.68; 95%CI 0.5-0.93; $p = 0.014$). The median time to radiologic progression was 2.8 months compared to 1.4 months in the placebo group ($p < 0.0005$). Although, the results observed from both studies were not similar in term of absolute survival, which was greater in the first study, the calculated reduction in

risk of death from the hazard ratio was comparable. At baseline the patients from the Asian-Pacific study had more extra-hepatic spread, higher tumor numbers, poorer performance status, higher alpha-fetoprotein level and more patients with HBV infection than in the Western study. These differences could explain the disparity in absolute survival between the two studies.

Sorafenib was generally well tolerated in both previous studies (Llovet et al., 2008; Cheng et al., 2009). The most common grade 3 drug-related adverse events included diarrhea (8%), and hand-foot skin reaction (8%). The adverse drug events led to dose reductions and interruptions, but rarely led to treatment discontinuation. The rate of permanent drug discontinuation from adverse events was 11% in Sorafenib group, and 5% in placebo group. Most Sorafenib studies were done in patients with well-preserved liver function, specifically Child-Pugh class A. However, Sorafenib had no significant pharmacokinetic difference between Child-Pugh class A and B patients (Abou-Alfa et al., 2006). The safety profiles were comparable between both groups (Lencioni et al., 2012). Hence, the discontinuation rate from adverse event was more common in Child-Pugh B. The short overall survival and toxicity reflecting worsening liver function were also more common in Child-Pugh B group (Abou-Alfa et al., 2006; Lencioni et al., 2012; Kim et al., 2011). HCC patients with poor liver function will not likely to get significant benefit from Sorafenib because of the high mortality from the decompensated cirrhosis.

Combination of Sorafenib and TACE

After successful TACE, the tumor undergoes necrosis, however this process is rarely completed because of angiogenesis process. The vascular endothelial growth factor (VEGF) has been found to increase locally and systemically after TACE treatment (Li et al., 2004; Wilhelm et al., 2008). Sorafenib can inhibit the activity of VEGF receptors.

A prospective, nonrandomized, comparative study in China compared the impact of concurrent TACE and Sorafenib vs. TACE alone in unresectable HCC patients with preserved liver function (Yao et al., 2011). Sorafenib was initiated within 1 week before or after the initial TACE treatment and continued throughout the study period in the absence of any intolerable adverse event. The median overall survival in the combination group (21.7 months, 95%CI 18.3-25.1) was better than the TACE alone group (11.5 months, 95%CI 7.8-12.5). The time to progression of tumor was significantly higher in combination group compared with TACE alone (10.2 months, 95%CI 9.7-10.7 vs. 6.7 months, 95%CI 6.1-7.2, respectively). The average interval to TACE, which was calculated as time to progression divided by the frequency of TACE treatment was also longer in the combination group ($p < 0.001$).

A meta-analysis of combination therapy of Sorafenib and TACE for unresectable HCC concluded that combination therapy may be superior over TACE alone in terms of time to progression but not overall survival (Liu et al., 2014). The adverse events seen in the study were considered to be generally manageable with dose reduction.

Treatment of HCC Complications

Spontaneous rupture of HCC is a relative uncommon but potentially life threatening complication. The incidence is higher in Asia however with the decreasing trend probably due to early detection of the cancer. The incidence ranges between 2.3-26% (Yoshida et al., 2016). Patients usually present with abdominal pain (66-100%) or shock (33-90%) (Yoshida et al., 2016). Diagnosis could be done by ultrasound or CT scan. Abdominal paracentesis can confirm the diagnosis. A retrospective study revealed that the underlying disease of hypertension, liver cirrhosis, tumor size >5 cm., vascular thrombus and extrahepatic invasion were predictive of ruptured HCC (Zhu et al., 2012). The primary goal of management for ruptured HCC is hemostasis control. Tumor treatment should wait until patients become stable. Coagulopathy should be corrected. Hemostasis could be done by Transarterial embolization (TAE) or surgery. The reported success rate of TAE varied between 53-100% (Yoshida et al., 2016). Recurrent bleeding or liver failure could occur following successful TAE. The 2-, 4- and 6- cumulative survival rate were significantly better for surgery (60%, 60% and 60%, respectively), or TAE (30%, 20% and 20%, respectively) compared to supportive care group (8.7%, 0% and 0%, respectively) (Jin et al., 2013). The factor associated with post treatment mortality includes serum bilirubin, creatinine level and vasopressor use (Jin et al., 2013).

Best Supportive Care

Many patients with HCC are discovered late in their disease, and most have advanced liver cirrhosis or even liver decompensation. For the group who had terminal stage of HCC, the only treatment option would be best supportive care. A retrospective study in patient diagnosed with unresectable and untransplantable HCC treated with TACE revealed that more than half (57%) of them died from cancer progression, the rest (43%) died in the absence of tumor growth (Couto et al., 2007). In one study focusing on end of life care in patient with terminal stage HCC, data was collected retrospectively from 110 patients who were admitted at hospital base hospice in Taiwan. Ninety-four patients died at the hospital with the median survival time of 12 days. Seventy-six patients (69.1%) developed upper gastrointestinal or variceal bleeding. Eighty-four patients (76.4%) required opiates for pain control. The group with severe underlying portal hypertension and deteriorating liver function suffered more from complications of portal hypertension such as variceal bleeding, ascites, jaundice and hepatic encephalopathy (Lin et al., 2004). Healthcare personnel who take care of terminal stage HCC patients need to be aware of common symptoms and signs of HCC-related complications, as well as complications of portal hypertension. Patients may require multiple paracentesis or abdominal drainage placement for ascites despite diuretic use. Pain control will be needed with lower dosages than in other cancer population because of the poor liver function and risk of developing hepatic encephalopathy. Psychological symptoms and mental condition would be difficult to assess in terminally

ill HCC patients because they usually manifest with encephalopathy. Caregiver and family should be aware of what to expect near the end of patient's life.

Conclusions

HCC remains a fatal malignant liver cancer worldwide. Treatment in early stage focus on curative therapy including hepatic resection, liver transplantation and ablative therapy. In intermediated stage, TACE is the important treatment. New approach of treatment would be focused on combination therapy eg. TACE combined with sorafenib. In advanced stage, best supportive care in end stage of disease would be considered. Treatment of complications such as infection or ruptures of the tumor are important steps to rescue these critical patients. Therefore, future studies on management of this particular cancer are tremendously important to offer better outcome of treatment and prolong survival for HCC patients.

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