Treatment of Hepatocellular Carcinoma in Asia and Western Area

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Introduction

Liver cancer is the fifth most common cancer in men worldwide (523,000 cases/y, 7.9% of all cancers) and the seventh most common cancer in women (226,000 cases/y, 6.5% of all cancers) according to the International Agency for Research on Cancer.\(^1\) Annually, more than 560,000 people are diagnosed with liver cancer and approximately the same number die with it.\(^2\) Hepatocellular carcinoma (HCC) accounts for 85-90% of liver cancer and these two entities are often used interchangeably.\(^3\) Variations in the age-, sex-, and race-specific rates of HCC in different geographic regions are likely to be related to differences in the prevalence of hepatitis viruses in the populations, as well as the timing of the diagnosis. Nowadays, in spite of the attempts to promote common protocols,\(^4\) the therapeutic approach to HCC mainly depends on the local prevalence and accessibility of treatment modalities and still remains different among Eastern and Western countries.

The purpose of this review is to overview the differences and similarities in the approach to HCC between Eastern and Western countries.

Treatment algorithm

The treatment algorithms in Europe and North America were based on the Barcelona-Clínica Liver Cancer (BCLC) staging.\(^5,6\) The BCLC staging classification consists of stage 0 to D: for if early stage 0, tumor is single and small (<2 cm) and patient has well preserved liver function (Child-Pugh class A), may be treated by resection; for early stage A, tumors are few (3 nodules) and relatively small sized (<3 cm) or there are evidence of mild portal hypertension and hyperbilirubinemia, may be treated by liver transplantation or local treatment; for intermediate stage B, tumors are multinodular, may be treated by transarterial chemoembolization (TACE); for advanced stage C, tumor invade vascular structure of spread extrahepatic organ, may be treated by sorafenib, for terminal stage D, patients are poor performance status or worse liver function (Child-Pugh class C), they treated by best supportive care. These are very strict criteria, and only stage 0 and A are indicated for curative treatments and no other choices for each stages. Furthermore, no combination therapy is recommended according to the algorithm.

In Eastern area, Asian Pacific Association for the Study of the Liver (APASL) recommended consensus guideline for HCC.\(^7\) The treatment algorithm in the guideline is similar to BCLC stage, but the differences are mentioned about systemic therapy trial in addition to sorafenib in extrahepatic spread or vascular invasion. In the Japan Society of Hepatology (JSH) updated practice guideline for HCC,\(^8\) It mentioned about combination therapy with TACE and local therapy for few (<3 nodules) and medium sized (>3 cm) tumor. For multiple tumor, hepatic arterial infusion chemotherapy (HAIC) can be considered as well as TACE. Even if there are no vascular invasion or
extrahepatic spread, sorafenib treatment may be considered for multiple tumors refractory to TACE. When determining liver transplantation, the age is considered in addition to tumor status. Korean Guidelines do not propose a treatment algorithm, but defined curative and non-curative therapies to have an option to treat with more curative intent.

**Treatment modalities**

1. **Curative treatment**

1) **Resection**

Resection is the first line treatment option for patients with solitary tumor and very well preserved liver function. In Europe and the United States, assessing liver function is based on the presence of portal hypertension. Studies have shown that a normal bilirubin concentration, and the absence of clinically significant portal hypertension measured by hepatic vein catheterization (hepatic vein pressure gradient \( \leq 10 \, \text{mmHg} \)) are the best predictors of excellent outcomes after surgery, with almost no risk for postoperative liver failure.\(^9,10\) Such patients achieve a 5-year survival of better than 70%.\(^9,11\) In contrast, the majority of patients with significant portal hypertension will develop postoperative decompensation with a 5-year survival of less than 50%. Clinically significant portal hypertension may also be suspected when the platelet count is below 100,000/mm\(^3\) associated with significant splenomegaly.\(^10\) Many Japanese groups rely on the indocyanine green retention rate at 15 min (ICG15).\(^12\) The decision whether surgery is feasible and the extent of the resection that can be performed is made based on the degree of retention of the dye.\(^13\) However depending on the number, location, and size of the tumor, extent of resection and residual liver function is different, and where deceased donor liver transplantation is not feasible in, especially in Korea, selective resection can be considered in Child-Pugh class A and upper B in patients with portal hypertension or mild hyperbilirubinemia.\(^14\)

Tumor size is also important prognostic factor. Five year survival rates for patients with HCC \( \leq 2 \, \text{cm} \) was of 66%, compared with 52% for tumors 2–5 cm and 37% for tumors >5 cm. Multinodularity also predicts survival, with 5-year survival rates after resection of single tumors of 57% and 26% for three or more nodules, respectively.\(^15-17\) However, it has been shown that patients with a large solitary HCC are suitable for successful resection and reasonable long-term survival results can be achieved.\(^18,19\)

Neo-adjuvant or adjuvant therapies have not proven to improve outcome of patients treated with resection. There were several studies of adjuvant therapy with vitamin K analogue in the patients with HCC after resection or ablation in Japan.\(^20-23\)

2) **Liver transplantation**

In most Asian area, the incidence of deceased organ donors remains below 5 per million per year.\(^24\) Because hepatitis B virus (HBV) is prevalent in most Asian area and 80% of HCC occurs in endemic area, HCC patients in Asian have a low probability of receiving deceased donor liver transplantation (DDLT) in time before tumor progression.\(^25\) As a result, development of living donor liver transplantation (LDLT) has accelerated. In Korea, the proportion of adult LDLT recipients with HCC has increased to 30–40%.\(^26\) In U.S.A., The number of donations from living donors reached a plateau at about 250, about half the number of a decade ago according to annual
The gradual decrease in the number of living donors in the US over the past 10 years may be related to concerns about donor safety. Morbidity rates for living donors remain relatively low, biliary complications are reported in less than 3% and vascular complications remain less than 2% in the first 6 weeks, and the frequency of reoperations in the first 6 weeks is low, at less than 4%. Unfortunately, two donor deaths were reported in 2010, and these deaths clearly affected the views of the transplant community regarding living donation. The European Liver Transplant Registry (ELTR) has cumulated data concerning 3622 LDLT performed in 78 centers from 20 countries from October 1991 to December 2009. It corresponds to 6.5%, 3622 of 47651, of total liver transplantation in Europe in last 10 years. The use of LDLT remains very limited, with a dramatic decrease during the past 5 years especially in European countries. Although the donor risk can be minimized at experienced centers, it does remain unacceptable for many transplant teams, especially if there is a significant risk of post-transplant recurrence.

The Milan criteria have been a reliable guideline for a long time. However, there are many volunteers lost opportunities because of the strict criteria. A few expanded criteria have been proposed, without significant increase in the risk of HCC recurrence. Lee et al. proposed expanded criteria of tumor diameter ≤5cm and number of lesions ≤6 with no macrovascular invasion. The number of patients was 211; the proportion of HBV 93%; 3- and 5-year survival rate was 87.5% and 81.6%, respectively. Ito et al. proposed tumor diameter ≤5 cm and number of lesions ≤10 with protein induced by vitamin K absence or antagonist-II (PIVKA-II) ≤400 mAU/mL. The number of patients was 125; the proportion of HBV 34%, HCV 53%; 5-year survival rate was 86.7%. It is remarkable for including the biological marker in addition to the tumor size and number. Expanding criteria is evaluated in West also. The proposed University of California, San Francisco (UCSF) criteria: a solitary tumor less than 6.5 cm or 2 or 3 nodules with the largest lesion less than 4.5 cm and a total of 8 cm, resulted in survival rates of 75% at 5 years. Some LDLT centers in Korea and Japan have challenged the Milan criteria, accepting a much higher number of HCC nodules (5 or more). On the other hand, a number of DDLT centers in West have mainly focused on expanded criteria regarding the tumor diameter (more than 5 cm).

Bridge therapy using local ablation or chemoembolization may reduce dropout rate with long waiting time of more than 6 months, but there is no proven benefit in long-term survival or downstaging to allow expand indication.

3) Locoregional therapy

Local ablation is considered for the patients with small HCC not suitable for resection. Radiofrequency ablation (RFA) is recommended in tumors less than 2 cm due to more predictable in all tumor sizes and its efficacy is clearly superior to that of ethanol injection in large tumors. Percutaneous ethanol injection (PEI) achieves necrosis rate of 90-100% of tumor <2 cm, but the necrosis rate is reduced to 70% in tumor 2-3 cm and to 50% in tumor 3-5 cm. In tumor ≤3 cm, 1-, 2-, and 3-year local recurrence rates were 10%, 14%, and 14% in the RFA group, 16%, 34%, and 34% in the PEI group (P=0.012). In tumor ≤4 cm, the rate of complete tumor necrosis was 88% in PEI, and 96% in the RFA group. PEI is recommended in cases where RFA is not technically feasible. In tumors <2 cm, both techniques achieve complete responses in more than 90% of cases, with a local recurrence rate of less than 1%. Whether they can be considered as competitive alternatives to resection is uncertain.
2. Palliative therapy

1) Transarterial chemoembolization

Transarterial chemoembolization (TACE) is recommended for patients with multinodular asymptomatic tumors without vascular invasion or extrahepatic spread. TACE is discouraged in patients with decompensated liver disease, severe liver dysfunction, macroscopic invasion or extrahepatic spread. TACE achieves partial responses in 15-55% of patients, and significantly delays tumor progression and macrovascular invasion. Meta-analysis of seven randomized controlled trials (RCT), including a total 516 patients, showed a beneficial survival effect of embolization/chemoembolization in comparison to the control group.

Although TACE has been known as contraindication in the case of HCC with portal vein invasion, recent studies report that TACE can be safely done and may achieve even survival benefit in the patients with preserved liver function. Especially when tumor is nodular and restricted in one lobe or 1-2 segments and liver function is preserved as Child-Pugh class A, the median survival of TACE group was 22-30 months, so intensive treatment is needed.

The ideal TACE scheme should allow maximum and sustained intratumoral concentration of the chemotherapeutic agent with minimal systemic exposure, along with calibrated tumor vessel obstruction. This strategy has been shown to increase the local concentration of the drug with negligible systemic toxicity. A randomized phase II study comparing TACE and TACE-DEB reported a significant reduction in liver toxicity and drug-related adverse events for the latter arm, associated with a non-significant trend of better antitumoral effect. There were relatively many studies in the West than the East. The median survival was 12-48 months and about 15 months in the Western and Eastern studies, respectively. There were experimental study of combination of DEB and sorafenib in patients with advanced HCC.

Internal radiation with Iodine-131 (\(^{131}\text{I}\)) or Yttrium-90 (\(^{90}\text{Y}\)) glass beads has shown promising antitumoral results with acceptable safety profile, but cannot be recommended as standard therapy.

2) Systemic therapy

Sorafenib is the standard systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh class A) and with advanced tumors (BCLC C) or those tumors progressing upon loco-regional therapies. Sorafenib has shown survival benefit in two randomized, placebo-controlled trials. In a large randomized placebo controlled trial (SHARP), the benefit of sorafenib was to increase the median overall survival from 7.9 months in the placebo group to 10.7 months in the sorafenib group (HR=0.69; 95% CI, 0.55-0.87; \(P=0.00058\)), which represents a 31% decrease in the relative risk of death. In addition, sorafenib 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. The magnitude of survival benefit was similar to that demonstrated in a parallel phase III trial conducted in the Asian-Pacific population, in which hepatitis B was the main cause of HCC. In this later trial, the median overall survival was 6.5 months in the sorafenib group versus 4.2 months in the placebo group (HR=0.68; 95% CI, 0.50-0.93; \(P=0.014\)). The worse outcome of patients included in this trial, regardless of treatment allocation, compared with the SHARP investigation, is due to the fact that the patients had more advanced diseases (ECOG 1-2 or metastatic disease).

In Asia, the underlying etiology of HCC is more attributable to HBV, ill-defined tumor types are more preva-
lent, and the prognosis of HCC is generally worse than in Western area, and the high cost of sorafenib is an obstacle to its use in clinical practice, Therefore, the development and customization of a rational approach based on cost, quality of life, and survival are needed.

Systemic chemotherapy, tamoxifen, immunotherapy, anti-androgen, and herbal drugs are not recommended for the clinical management of HCC patients.

There is no available second-line treatment for patients with intolerance of failure to sorafenib. Patients at BCLC D stage should receive palliative support including management of pain, nutrition, and psychological support.

3) Radiotherapy

The use of conventional external-beam radiation therapy in HCC treatment has been limited by the low radiation tolerance of the cirrhotic liver, which often resulted in radiation-induced liver disease, previously known as radiation-induced hepatitis. The benefits of external three-dimensional conformal radiotherapy have only been tested in uncontrolled investigations.

Radiotherapy can be used to alleviate pain in patients with bone metastasis. The pain relief after radiotherapy for bone metastasis of HCC has been reported about 75-84%.

Radiotherapy can improve the symptoms in the cases of jaundice, symptomatic biliary obstruction due to tumor lesions. In the studies of Korea, radiotherapy induced 40-50% of tumor responses and the median survival was about 10-13 months in the patients with HCC with macrovascular invasion.

In the cases of small HCC, if resection or RFA is difficult due to location of the tumor, stereotactic body radiation therapy (SBRT) can achieve high locoregional control of tumor.

Proton beam therapy (PBT) has the theoretical advantages into less damage to surrounding liver tissue and its geophysical characteristics that can maximize the effect on the tumor.

3. Experimental therapy

1) Chemotherapy

The problem of using chemotherapy in HCC arises from the co-existence of two diseases. Cirrhosis can perturb the metabolism of chemotherapeutic drugs and enhance their toxicity. On the other hand, HCC has been shown to be chemoresistant to the most common chemotherapies. The tumor response rate to single-agent cytotoxic therapies is usually less than 10%, and no survival benefit has been observed. An earlier randomized trial comparing doxorubicin, 60-75 mg/m² every 3 weeks, with no treatment indicated a borderline improvement in overall survival (10.6 vs. 7.5 weeks) for patients who received doxorubicin. However, 25% of patients died of doxorubicin-related complications, including infection and cardiotoxicity. The antitumor activity of other cytotoxic agents, such as gemcitabine, oxaliplatin, and capecitabine, has been modest, with single-agent tumor response rate of 10% or less. A large RCT which compared combination chemotherapy (Cisplatin/Interferon a2b/Doxorubicin/Fluorouracil-PIAF regime) versus doxorubicin chemotherapy showed objective response rates of 20.9% and 10.5%, respectively. The median survival of the PIAF and doxorubicin groups was 8.67 months and 6.83 months, respectively without differences between groups. A second RCT conducted in Asia compared the efficacy of the Folfox regimen combining 5-fluorouracil, folic acid and oxaliplatin against doxorubicin alone. This study included 371 patients with Child-Pugh A/B advanced non-operable metastatic HCC (BCLC B/C). There was a non-significant trend favoring the Folfox group (median survival 6.4 mo versus 4.9 mo; \( P=0.07 \)) associated
to a better time to progression (2.9 mo versus 1.7 mo). Therefore, systemic cytotoxic chemotherapy in HCC should be limited to patients with favorable liver function and general condition, and in some cases, to avoid compromising the quality of life the use of less toxic drugs or a dose reduction is needed.

Conclusions

Main policies for treatment of HCC are not much different world-wide as tumor stage, liver function, and performance status are the main determinants for therapeutic decision. However, differences according to the available resources definitely exist. Currently, several treatment modalities which have been considered experimental therapies are used for definite treatment of HCC as well as palliative therapy. Combining the Western and Eastern experiences for HCC treatment and co-efforts to determine the best way to treat HCC will lead to establishment of world-wide consensus in this field.

References


The Korean Association for the Study of the Liver

SYMPOSIUM 3

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