Juniper publishers
key to the Researchers

Anatomy Physiology & Biochemistry
International Journal
ISSN: 2476-1400

Review Article
Volume 1 Issue 2 - February 2016

Canc Therapy & Oncol Int J

Current Standards of Systemic Therapies in Advanced Hepatocellular Cancer: A Review

Hossam Hosny*

Orthopaedic Surgery Department, Sohag University, Egypt

Submission: February 22, 2016; **Published:** February 25, 2016

***Corresponding author:** Hossam Hosny, Assistant lecturer of Orthopedic Surgery, Orthopaedic Surgery Department, Sohag Faculty of Medicine, Sohag University, Sohag 82648, Egypt, Tel: 201009341779; Email: hosam09@yahoo.com

Abstract

Sorafenib a multikinase inhibitor is the only approved systemic therapy in the treatment of advanced hepatocellular cancer. No other targeted therapy have proved to be better, a lot of phase 3 trials with many targeted have shown no significant or clinically relevant activity. After SHARP trial no other trial with any other targeted therapy has shown any significant improvement in the treatment of hepatocellular cancer. EACH trial, a phase 3 randomized trial conducted on Asian patients proved better RR and PFS of FOLFOX4 regimen when compared to doxorubicin, showed efficacy and safety of FOLFOX4 protocol. In the light of so many negative phase 3 trials with targeted therapies, it seems only sorafenib still can be considered a standard therapy in advanced HCC.

Abbrevitions: Hepatocellular cancer (HCC); OS-overall survival; PFS-progression free survival; SHARP trial; EACH trial

Introduction

Hepatocellular cancer is the fifth most cancer worldwide, third leading cause of cancer death worldwide as shown by most recent World health Organization data [1]. Highest incidence is being observed in Asia followed by Western Africa. Although the incidence is increasing, but amount of HCC related deaths are stabilizing and even decreasing in some Asian studies, thanks to better treatment options, improved surveillance and due to extensive aggressive Hepatitis B Virus vaccination programs. On the contrary there has been an increase in mortality rates in the Western World. Hepatitis B virus, Hepatitis C virus are the most common etiological agents which cause chronic liver injury which causes cirrhosis. Cirrhosis being the most common finding hepatocellular cancer can be found in 95% of patients of chronic Hepatitis C and in chronic Hepatitis B cancer patients. Heavy intake of alcohol may cause cirrhosis, if it occurs with co-existent Hepatitis C - the risk of having hepatocellular cancer is the 2 fold as compared to risk of developing HCC only after prolonged abuse of alcohol. Hereditary Hemochromatosis induced cirrhotic rise of diabetes mellitus and obesity in the world, there has been rise in nonalcoholic steatohepatis associated HCC. Geographical areas which have high exposure to aflatoxin B1 have high incidence of HCC.

Staging of Hepatocellular Cancer

Currently the most accepted if not the world over, at least in the western world is the Barcelona Clinic Liver Cancer staging system [2]. BCLC staging system was developed based on the retrospective analysis of various HCC studies and incorporated patients in early, intermediate and advanced terminal disease. BCLC staging not only stages the patients to: early, intermediate, advanced and terminal stages but also recommends treatment modalities and also offers prognostic estimates. For early stages liver transplantation, liver resection, radiofrequency ablation offer a 5 year survival rate of 50-75%.In intermediate BCLC stage - the survival beyond 3 years is not observed in 50% of cases, if no therapy is offered so these patients are candidates for TACE. In advanced disease survival beyond 1 year is not observed in 50% of cases. These patients are rendered candidates for treatment with sorafenib or for therapeutic clinical trials. For end stage disease symptomatic treatment is provided.

Treatment

Depending on the disease stage different treatment modalities are chosen. For example in early stages liver resection in non cirrhotic patients being the choice , but only 10-30% patients are suitable candidates such a treatment modality. Milan criteria

[3] introduced by Mazzaferro and Bismuth following their landmark studies produced excellent results in liver transplant patients with solitary HCC <5cm or with up to 3 nodules <3cm. Afterwards Yao et al.'s [4] group from the University of California San Francisco (UCSF) expanded the selection criteria for liver transplantation. They proposed that solitary tumours ≤6.5cm, the presence of 3 or fewer nodules (with the largest lesion ≤4.5cm), or a total tumour diameter ≤8cm, without evidence of gross vascular invasion should be included in the criteria. Percutaneous ablation is the treatment choice for early stage HCC who are not candidates for liver transplantation and for liver resection. Sometimes, this treatment modality is used as a bridge to liver transplantation. Radiofrequency ablation is proffered mode of treatment, than percutaneous alcohol injections as local therapies as RFA provides improved tumor response and long term survival [5,6]. Transarterial Embolisation / Transarterial Chemoembolisation offers 5 year survival in more than 50% to patients who are not candidates for liver resection, liver transplantation or for radiofrequency ablation. TAE/ TACE can be done in patients who have maintained portal blood flow and in the absence of extrahepatic tumour spread. As far as approved therapies are concerned only Sorafenib is the only approved drug for advanced HCC world over following the success of SHARP trial, more recently EACH trial [7] in the east has showed promising results -improvement in RR and PFS showing FOLFOX4 being a promising regimen. Following EACH trial oxaliplatin was approved by China Food and drug administration for advanced HCC.

Systemic Therapies

As shown in the landmark SHARP phase III trial (Sorafenib HCC Assessment Randomized Protocol), sorafenib has demonstrated to increase overall survival from 7.9 months to 10.7 months and prolonged the median time to disease progression when compared with the control group [5]. Thus till date Sorafenib is the only approved a drug in the West. Cheng et al. [6] showed similar results with Sorafenib as shown in their Asia Pacific population. More recently EACH trial has also shown promising results among Asian patients .EACH trial was a phase 3 trial conducted on Asian patients with advanced hepatocellular cancer patients. This trial showed that FOLFOX4 regimen improved RR and PFS/DCR when compared to doxorubicin alone. It seems that FOLFOX4 regimen can also be a promising protocol in the treatment of advanced hepatocellular carcinoma. FOLFOX4 can be promising in the light that many phase 3 trials with targeted therapies have proved to be negative trials. After Sorafenib no new targeted agent has shown significant clinical activity.

Chemotherapy

Protocol FOLFOX4

EACH trial was a phase III open label randomized study conducted in mainland China, Taiwan, Korea and Thailand which included 371 patients.184 patients were on FOLFOX4 arm and 187 patients were on Doxorubicin arm. The treatment was continued until progression, toxicity, death or until patient was rendered eligible for resection. As far as objectives of this study are concerned, the primary endpoints were to determine whether FOLFOX4 improves overall survival (OS) compared to doxorubicin. The secondary endpoint was to compare the efficacy and safety of the two treatment regimens to evaluate PFS, RR, DCR by RECIST. Also the safety criteria were seen as per NCI-CTC AE v 3.0.

The results of this phase 3 trials seems to be interesting as the trial showed improved RR and PFS , and among the chinese patients an improved OS was observed in the FOLFOX4 arm.

Protocol GEMOX

Loufi et al. [8] (Cancer, 2007, 109, 1384-1390) showed in a phase II study using GEMOX (Gemcitabine plus oxaliplatin) in advanced HCC where RR was 18% , stable disease was shown on 58% patients, the progression free survival observed was 6,3 months, and median OS observed was 11,5 months. The treatment was well tolerated. Severe thrombocytopenia (grade III/IV - NCI/CTC) was observed among 27% patients, severe neutropenia (grade III/IV- NCI/CTC) among 24% patients, grade III/IV anemia observed in 9% and neurotoxicity among 9% patients.

Other chemotherapeutic agents: Doxorubicin, Cisplatin, etc. have also been used in the treatment of advanced HCC either not showing any significant clinical activity.

Targeted Therapies

Sorafenib

Sorafenib is a multikinase inhibitor that blocks both the tumour cell proliferation and also exerts antiangiogenic effects. This is achieved through inhibition of the Raf/mitgen-activated protein kinase/extracellular signal-regulated kinase (Raf/MEK/ERK) signaling pathway and action against the VEGF-2, VEGF-3 and PDGF receptors. Sorafenib is a multikinase inhibitor, inhibiting several receptor tyrosine kinases and serine / tyrosine kinases. The tyrosine kinases blocked are RTK, VEGFR-1, VEGFR-2,VEGFR-3, FLT-3, RET, PDGFR-beta, C-kit, FGFR-1, c-met, IGFR, EGFR-1, HER-2, LCK. The serine/threonine kinases blocked are Raf -1, beta RAF, R- raf, p 38, Mnk-2, ERF, MEK-1, PKA, PKC cdk1, cyclin B, pin.

Sorafenib was approved on the basis of landmark SHARP phase III trial (SHARP-Sorafenib HCC Assessment Randomized Protocol, Llovet et al. [5] NEJM 2008; 359-378-90), sorafenib demonstrated increase of overall survival from 7.9 months to 10.7 months and prolonged the median time to disease progression when compared with the control group. Due to clear improvement in overall survival this trial was completed

How to cite this article: Hossam H. Current Standards of Systemic Therapies in Advanced Hepatocellular Cancer: A Review. Canc Therapy & Oncol Int J. 2016; 1(1): 555551. DOI: 10.19080/APBIJ.2016.01.555551.

only at it's interim analysis due to breakthrough data presented by Llovet et al. [5] Another study by Cheng et al in the east was done which showed similar results with Sorafenib among Asian patients.

The subgroup analysis of this trial showed that as far as that in the trial population (n=602) Sorafenib showed an improved survival (10,7 months vs 7,9 months). Sub analysis further showed that for patients who had undergone prior curative therapy (n=158) in the Sorafenib arm the median survival was 11,9 in the Sorafenib arm vs 8,8 month in the placebo arm. Patients who had prior TACE (n=176) in the Sorafenib arm showed OS of 11,9 months vs 9,9 months in the placebo arm. Patients who had HCV infection (n=178) showed OS of 14,0 months in the Sorafenib arm vs 7,0 months in the placebo arm. For patients with cirrhotic analysis (n=159) OS was 10,3 month in Sorafenib arm vs 8,0 month in placebo arm. In patients with good performance status ECOG-0 (n=325) showed OS of 13,3 months in Sorafenib arm vs 8,8 months in placebo arm. For ECOG 1-2 (n=277) the OS was 8,9 months in the Sorafenib arm vs 5,6 months in the placebo arm.

Molecular targeted therapies in HCC

Many novel targets are: mTOR, MEK, IGFR-1, MET , FGF , TIE-2, HDAC. In advanced HCC many molecular therapies were tested for HCC in phase III trials [9] with advanced HCC as first line. Agents being tested are therapy with sorafenib and erlotinib put together. In other trials Sorafenib was compared with Brinavib alone, with Sunitinib alone, with Linifarib alone, with lenvatinib .Other trials evaluated Sorafenib with yattrium -90, others evaluated Sorafenib given with doxorubicin vs Sorafenib alone.

Cheng et al. [10] conducted a phase 3 trial comparing sunitinib with sorafenib where median survival for sunitinib arm was 7,9 months vs 10,9 months in the sorafenib arm. Thus was declared a negative trial [10].

Zhu et al. [11] conducted a phase III trial evaluating sorafenib along with erlotinib put togethet vs sorafenib (standard drug) alone. Primary endpoint was OS (superiority).This too was a negative trial as in the sorafenib and erlotinib arm the TTP was 3,2 months vs 4,0 months in sorafenib alone arm [11-13].

Johnson P et al. [14] in a phase III trial (non inferiority design) showed whether the primary endpoint was overall survival, the trial evaluated sorafenib with brivanib. In the sorafenib arm OS observed in the sorafenib arm was 9,9 months, and in the Brivanib arm the median overall survival observed was 9,5 months. Thus was also a negative trial. Other first line treatment phase III trial for advanced hepatocellular cancer evaluating linifanib [12] comparing with standard drug Sorafenib was also negative.

On the second line treatment Llovet et al. [5] evaluated Brivanib [13] in second line vs placebo where it was found that the median OS for Brivanib was 9,4 months vs 8,2 months in the placebo arm.

In the REACH study (Zhu et. al. [11] Annals of oncology, 2015) Ramucirumab which evaluated patients with advanced HCC following treatment with sorafenib, as a second line drug Ramucirumab was evaluated which did not show any significant improvement in OS. However in this study a clinically consistent and clinically meaningful improved OS was observed in ITT patients with baseline AFP levels more than or equal to 400ng/ml with similar trend in Child Pugh B patients. In the ITT population with baseline AFP more than or equal to 400 ng/ml, a strong trend for delay in symptoms and delay in PS deterioration was observed. The safety profile of Ramucirumab was manageable regardless of baseline AFP. The overall survival in Ramucirumab arm was 9,2 months vs 7,6 months. Thus this was also a negative trial.

Other phase III trials evaluated Brivanib, Everolimus and Ramucirumab in second line did not show any cinically significant or clinically relevant results. Recently El. Khoueriry et al. at ASCO 2015 showed a phase I/II trial with Nivolumab (anti PD), and showed ORR in 8 out of 44 patients (19%). evaluated by RECIST and OS -62% at 1 year.

Discussion

After having had so many failures except with Sorafenib in the treatment of advanced hepatocellular cancer, especially while evaluating targeted therapies in advanced HCC, it makes us think why many of these targeted therapies do not work. Answer is maybe, because there is a poor understanding of the disease overall, many a times it's one a single disease, it is advanced HCC with cirrhotic liver disease. And in such a situation we have to make a balance between efficacy and toxicity (sunitinib, linifanib). Many trials were designed with non inferiority concept (Brivanib, linifanib). Other reasons maybe that the phase III trials were planned with targeted therapies which did not show any significant promise / efficacy in phase II. Thus the drugs used in phase III trials were not powerful enough, so they did not show any significant clinical activity. (examples being brivanib, linifarib, erlotinib, everolimus, ramucirumab). As far as sorafenib is concerned biomarkers predicting response to sorafenib are unknown. So seeing a lot of failures it makes us look to classical chemotherapies, may be they can prolong OS if given along with these targeted therapies. Thus trial conducted in Asia EACH trial, phase 3 trial (Qin S et. al. [12] JCO 2013) which showed superiority of FOLFOX4 over doxorubicin, showed improved PFS and RR in the FOLFOX4 arm can prove to be breakthrough event in the treatment with advanced HCC. China Food and Drug administration following the data provided by EACH trial approved the drug oxaliplatin for the treatment of advanced hepatocellular cancer. It also seems that future may lie in combining chemotherapy with targeted therapies.

Conclusion

Thus it seems that since sorafenib is the only approved drug for patients with advanced HCC, till date only sorafenib is the

How to cite this article: Hossam H. Current Standards of Systemic Therapies in Advanced Hepatocellular Cancer: A Review. Canc Therapy & Oncol Int J. 2016; 1(1) : 555551. DOI: 10.19080/APBIJ.2016.01.555551.

drug which remains the drug of choice in first line treatment of advanced HCC. In cases where treatment with Sorafenib not possible, in present clinical practice it seems that off label usage of oxaliplatin containing protocols like GEMOX or FOLFOX4 in the light of data provided by EACH study can be justified. Oxaliplatin is an approved drugs in certain parts of our world after conducting randomized phase 3 trials. There exists a need to validate this data by conducting prospective phase III randomized trials in the West. In west the etiology is a bit different (alcohol, Hepatitis B virus) than in parts of Asia (Hepatitis C virus, aflatoxins) thus the observations sought by our Asian colleagues seem to be very promising but need validation in the west.

References

1. Jong-wook L (2003) Global health improvement and WHO: shaping the future. Lancet 362(9401): 2083-2088.
2. Llovet JM, Bru C, Bruix J (1999) Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 19(3): 329-338.
3. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, et al. (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334(11): 693-699.
4. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, et al. (2001) Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 33(6): 1394-1403.
5. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, et al. (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359(4): 378-390.
6. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, et al. (2009) Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10(1): 25-34.
7. Qin S, Bai Y, Lim HY, Thongprasert S, Chao Y, et al. (2013) Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. J Clin Oncol 31(28): 3501-3508.
8. Loufi et al. (2007) Cancer 109(384): 1390-1399.
9. Clinical trials.gov
10. Cheng AL, Kang YK, Lin DY, Park JW, Kud M, et al. (2013) Sunitinib vs Sorafenib in advanced HCC: results of a randomised phase III trial. J Clin Oncol 31(32): 4067-4075.
11. Zhu AX, Rosmorduc O, Evans TRJ, Ross, Santoro A, et al. (2012) SEARCH : Phase III randomised , double blind placebo- controlled trial of sorafenib plus erlotinib in patients with hepatocellular cancer(HCC). aNNAL OF oNCOLOGY 23(sUPL. 9): ixe1-ixe30.Abstract LBA2.
12. Cainap C, Qin S, Huang WT, Chung IJ, Pan H, et al. (2012) Phase III trial of linifarib versus sorafenib inpatients with advanced hepatocellular cancinoma (HCC). J Clin Oncology 30(suppl 34): Abstract 249.
13. Chinese Ministry of Health (2011) Diagnosis and treatment guideline of primary liver cancer. Chinese Ministry of Health, Beijing, China.
14. Abou-Alfa GK, Johnson P, Knox JJ, Capanu M, Davidenko I, et al. (2010) Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: A randomized trial. JAMA 304(19): 2154-2160.

How to cite this article: Hossam H. Current Standards of Systemic Therapies in Advanced Hepatocellular Cancer: A Review. Canc Therapy & Oncol Int J. 2016; 1(1): 555551.