<u>Review Article</u>

SORAFENIB IN HEPATOCELLULAR CARCINOMA: HYPE OR HOPE?

SOMSUVRA B. GHATAK*, SHITAL J. PANCHAL

Department of Pharmacology, Institute of Pharmacy, Nirma University, Sarkhej-Gandhinagar Highway, Ahmedabad-382 481, Gujarat, India. Email: ghataksom16@gmail.com

ABSTRACT

Hepatocellular carcinoma (HCC) is the fifth most commonly prevalent tumor worldwide and continues to have a dismal prognosis with an expected survival of 4-6 months. Effective systemic treatment options for advanced HCC are limited and its management is still a challenge to the physicians since these patients are not the potential candidates for surgical or ablative therapy. Sorafenib, an oral multikinase inhibitor, previously tested and found effective against other solid tumors, has been proven to be the first targeted therapeutic option to demonstrate a survival benefit for the treatment of advanced HCC via favorable effects on both proliferation and angiogenesis. However, additional controlled studies are awaited on the role of this agent in patients with advanced liver disease and as an adjunctive therapy in combination with other modalities, targeted at the multiple carcinogenic pathways involved. This contribution provides a comprehensive review of sorafenib, as a valuable option to significantly extend survival for patients with advanced HCC, with the results obtained from large-scale, randomized trials as its vivid backdrop.

Keywords: Hepatocellular carcinoma, Kinase inhibitor, Sorafenib

INTRODUCTION

Hepatocellular carcinoma (HCC), considered as one of the most common malignant tumors worldwide, represents an estimated 500 000 to 1 million new cases per year.[1] Considered as a common complication of chronic liver diseases, HCC has an age-adjusted annual incidence between 5.5 and 14.9 people per 100,000 population, resulting in approximately 600,000 to 1,000,000 deaths annually.[2-5] Having a dismal prognosis with a 5-year survival of 1–4%, HCC represents the third leading cause of cancer death worldwide with an approximate 77% of deaths occurring in the developing countries.[6,7]

Most Asian countries are in intermediate (between 5 and 15 per 100 000 population per annum), or high (>15 per 100 000 population per annum) incidence zones of HCC.[8] In line with this, the prevalence of HCC in India varies from 0.2% to 1.6%, with the mean incidence in four population-based registries being 2.77% and 1.38% for males and females respectively.[9,10]

Furthermore, the predominant etiological factor associated with HCC in India is the hepatitis B virus (HBV) infection.[11-15] In the west, majority of HCC diagnosis is incidental during routine evaluation. However, in India, most of the patients in clinical practice present at an advanced stage, thereby ruling out curative treatment in most cases.

In view of the lethality, invasiveness of the cancer and the compromised hepatic function from the underlying liver disease, HCC has long been perceived as a particularly challenging disease to treat. The inelasticity of the cirrhotic liver and the failure of tumor death to lead to lesion shrinkage, even in presence of substantial tumor necrosis have made the response rate and the conventional go/no-go decision maker from phase II trials an unreliable surrogate for HCC. The challenge of intrinsic resistance to chemotherapy drugs in HCC can be attributed to an increased expression of multidrug resistance transporters and active intracellular metabolism.[16-18] The appropriate dosing of medications in HCC patients compared to phase I studies in patients with normal organ function is interrupted by an impaired liver function which subsequently complicates the interpretation of toxicities. The existing treatment modalities, including hepatic resection, ablative therapy (radiofrequency ablation and percutaneous ethanol injection) and orthotropic liver transplantation, although, are able to manage early HCCs with single lesion <5 cm or multiple HCCs that are less than three in number and <3 cm each, it is typically only the far advanced HCC patients with vascular invasion and multiple intra-hepatic metastases who are referred for systemic therapy.

However, despite an urgent need for new therapies for this aggressive disease, no systemic treatment has so far been demonstrated to confer a survival advantage or improved quality of life for patients with HCC in a randomized clinical trial, until the advent of sorafenib® (Nexavar, Bayer HealthCare Pharmaceuticals-Onyx Pharmaceuticals), an oral multikinase inhibitor, that was recently granted fast-track status in the setting of HCC.[19,20] The current review focuses exclusively on the major pharmacological features of sorafenib and its role in the management of advanced HCC, with special reference to the results obtained from the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP), a study comparing sorafenib with placebo in patients with HCC, thereby indicating it to be the first agent to demonstrate a survival benefit in this setting.[21]

About Sorafenib

Sorafenib, belonging to the bi-aryl urea class with a molecular weight of 637 g/mol, is a small orally available multikinase inhibitor that targets the serine-threonine kinase Raf-1 and possesses anti-angiogenic activity.[22-24]

Sorafenib is given at a dose of 400 mg twice daily with a mean bioavailability of 38-49% and a mean half life of 25–48 h. It undergoes hepatic metabolism by two pathways: oxidative metabolism mediated by cytochrome p450 (CYP3A4) and glucourinidation mediated by UGT1A9. Steady state plasma concentration is achieved within 7 days. No impact of renal function was observed on sorafenib steady state level in patients with creatinine clearance ≥30 ml/m in; however, there is paucity of data for patients with creatinine clearance < 30 ml/min or for those on dialysis. Moreover, there is no alteration in the sorafenib metabolism in patients with chronic liver disease (CLD) Child–Pugh (CP) classes A (well-compensated disease) and B (significant functional compromise), while no data is available for CP class C (decompensated disease) patients. Dose adjustment for sorafenib is not required for age, gender, body weight, and in patients with mild to moderate renal or hepatic impairment.[25,26]

Mechanism of Action

Angiogenesis as well as signaling through the RAF/mitogen activated protein (MAP)/extracellular signal-regulated kinase (ERK) kinase (MEK)/ERK (RAF/MEK/ERK) cascade play critical roles in the development of HCC. Hence, anti-angiogenesis therapies, capable of inhibiting blood vessel formation, may hold promise in the treatment of HCC, in view of the fact that a rich blood supply facilitates HCC tumor development.[27] Human HCC tumors, in addition to being highly angiogenic, have high expression and enhanced activity of MAP kinase (MAPK) as compared to the adjacent non-neoplastic liver.[28] Therefore, inhibition of both angiogenesis and RAF/MEK/ERK signaling may represent an attractive and viable approach for the treatment of HCC.

Sorafenib is a small molecule that blocks both tumor-cell proliferation and tumor angiogenesis by virtue of the inhibition of serine/threonine kinases (c-RAF, and mutant and wild-type BRAF) as well as the receptor tyrosine kinases vascular endothelial growth factor receptor 2 (VEGFR2), VEGFR3, platelet-derived growth factor receptor (PDGFR), FLT3, Ret, and c-KIT.[29,30] Published reports have further indicated that sorafenib inhibits the translation and down-regulation of myeloid cell leukemia-1 (Mcl-1), a Bcl-2 family member, thereby inducing apoptosis in human leukemia cells and other human tumor cell lines.[31,32]

Clinical Uses

Sorafenib was approved by the US-FDA in December 2006 for the treatment of advanced renal cell carcinoma (RCC) after demonstrating a two–fold increase in progression-free survival in 903 patients in a placebo-controlled trial. Stable disease was observed in 78% and 55% of patients on sorafenib and placebo respectively, while tumor shrinkage was observed in 74% of patients treated with sorafenib as compared to 20% of patients who received placebo.[33]

In a phase II trial, sorafenib also demonstrated a modest anti-cancer activity comparable to monotherapy with other targeted agents in patients with recurrent or metastatic squamous cell carcinoma of the head and neck or nasopharyngeal carcinoma.[34] Sorafenib in combination with gefitinib is also well tolerated, with promising efficacy in patients with advanced non mall cell lung cancer.[35] Furthermore, published literature reports have indicated the benefits of sorafenib in malignant melanoma, metastatic breast, prostate and pancreatic cancers and many trials are focused towards evaluating its efficacy in these conditions.[36-38]

Early Evidences in HCC

In preclinical experiments using a mouse xenograft model of HCC, sorafenib exhibited anti-proliferative activity in liver-cancer cell lines, and it reduced tumor angiogenesis and tumor-cell signaling and increased tumor-cell apoptosis.[39]

In a phase I setting, sorafenib demonstrated an acceptable safety profile as well as a partial response in a HCC patient.[40]

The phase II trial of 400 mg oral sorafenib twice-daily in 137 previously untreated patients with inoperable HCC (72% with Child-Pugh A disease, 28% with Child-Pugh B disease), resulted in partial response in 2.2% of patients, minor response in 5.8%, and stable disease for ≥ 16 weeks in 33.6%.[41] Median time to disease progression was 4.2 months, and median overall survival (OS) was 9.2 months, which was comparable to those of the best published combinations of systemic chemotherapy in advanced HCC.[41-43] Grade 3/4 drug-related toxicities included fatigue in 9.5%, diarrhea in 8.0%, and hand–foot skin reaction in 5.1% patients. Toxicity levels were also minimal in the way of conventional Response Evaluation Criteria in Solid Tumors (RECIST) responses. There were no significant pharmacokinetic differences between patients with Child-Pugh class A and B.

In patients with advanced HCC and Child-Pugh A, another phase II, randomized, double-blind study suggested improved outcomes in terms of prolonged overall survival (OS) and time to progression (TTP) with the addition of sorafenib to doxorubicin.[44]

Sorafenib Vs Placebo

The phase II trials of sorafenib were followed by the international, multicenter, randomized, double-blind, placebo-controlled, phase III Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, that enrolled 602 patients with advanced HCC and preserved liver function.[21]

The population comprised approximately 30% of patients with hepatitis C virus (HCV) infection, 20% with hepatitis B virus (HBV) infection, and 25% with alcoholic liver disease. Nearly all patients had Child-Pugh class A (CPA) cirrhosis, with Eastern Cooperative Oncology Group performance status score of 0 or 1. Patients were randomly assigned to receive sorafenib at a starting dose of 400 mg twice daily (n = 299) versus placebo (n = 303). The primary end

points were OS and TTP, and the patients could remain on treatment until they experienced disease progression both radiographically and symptomatically.

At the second planned interim analysis performed after 321 deaths (143 in the sorafenib group, 178 in the placebo group), overall median survival was significantly longer in the sorafenib group than in the placebo group (10.7 months vs. 7.9 months; hazard ratio in the sorafenib group, 0.69; 95% confidence interval [CI], 0.55 to 0.87; P<0.001). There was no significant difference between the two groups in the median time to symptomatic progression (4.1 and 4.9 months, respectively; hazard ratio, 1.08; 95% CI, 0.88 to 1.31; P = 0.77). With regard to the secondary endpoints, time to disease progression was significantly improved with sorafenib versus place-bo (5.5 vs. 2.8 months; hazard ratio, 0.58; 95% CI, 0.45 to 0.74; P<0.001); rates of disease control (defined as a complete or partial response or stable disease for 2 or more cycles) were significantly higher in the sorafenib group as compared to the placebo (43% v 32%; P=0.002).

Sorafenib showed a favorable safety profile and was well tolerated. The frequency of serious adverse events was 52% in the sorafenib group versus 54% in the placebo group; the most frequent grade 3/4 drug related adverse events were diarrhea (11% v 2%), fatigue (10% v 15%), hand-foot skin reactions (8% v 1%), and bleeding (6% v 9%).

Sharp Trial: A Critical Assessment

Although the SHARP study represents a clear paradigm shift in the role of chemotherapy for HCC, there are several key differences between the patients involved in the SHARP trial and those with advanced HCC in real clinical practice. While HCV and HBV were the causes of liver disease in approximately 30% and 20% of patients respectively in the SHARP study, more than 70% of the patients with HCC in the United States and western Europe test positive for HCV and 60% to 80% of HCC cases worldwide are positive for HBV infection.[45,46]

In the light of this dominance of HBV as the cause of HCC globally, the relative scarcity of such patients in the SHARP trial makes a subset analysis less statistically informative since it does not allow an assessment of the efficacy of sorafenib in HBV. Furthermore, contrasting results were observed in the Asian phase III, randomized, double-blind, placebo-controlled trial of sorafenib versus placebo in patients with advanced (unresectable or metastatic) HCC, wherein, more than 70% of the 226 patients were positive for HBV.[47] Median overall survival was 6·5 months (95% CI 5·56—7·56) in patients treated with sorafenib, compared to 4·2 months (3·75—5·46) in those who received placebo (hazard ratio 0·68 [95% CI 0·50—0·93]; p=0·014). The benefit, although is of the same relative magnitude as that observed with sorafenib in the SHARP trial, the patients in both the arms fare appreciably worse than those of SHARP. However, the underlying factors accounting for the differential outcomes between the Asian and the Westernized SHARP population is still unclear.

Moreover, 97% of the SHARP patient population classified as CPA diverges from the majority of patients with HCC by the limited extent of underlying liver dysfunction and such a study design potentiated the clinical benefit by minimizing the confounding variable of death from progressive liver disease.[21] Therefore, the study does not ascertain the safety or efficacy of sorafenib in patients with greater degrees of liver compromise. Contrasting results were however observed in the phase II study by Abou-Alfa et al (2006), where 28% of the patients were with CPB, and in spite of the similar pharmacokinetic profiles between the groups, OS was 14 weeks in the CPB patients compared to 41 weeks in the CPA patients.[41,48] Additional concerns for hepatic decompensation were observed in the study with sorafenib in regards to hyperbilirubinemia, encephalopathy and ascites in the CPB subgroup. Another study of sorafenib in 58 poor-risk patients, including 26% with CPB or worse liver function and 50% with portal vein thrombosis indicated an overall response rate of 20% with 34% of the patients experiencing grade 3 or 4 toxicity.[49] Such studies implicate the potential for significant toxicity and less clinical benefit

associated with sorafenib in patients with compromised hepatic function.

However, based on the findings obtained from the SHARP trial, sorafenib was approved by the US Food and Drug Administration (FDA) in November 2007 as the new reference standard of care for the first–line treatment of patients with advanced HCC. On the contrary, the more stringent practice guidelines by the National Comprehensive Cancer Network for patients with advanced HCC considers the sorafenib data as inadequate to define the dosing or safety in patients with CPB or worse liver function and emphasizes extreme caution in patients with elevated bilirubin levels.

CONCLUSION

Although the SHARP results can only be implemented to a minority of patients with advanced HCC at this point, sorafenib definitely offers real hope of efficacious treatment for patients with advanced HCC and preserved liver function, considering the current lack of effective therapies capable of significantly improving survival in liver cancer, and the well understood nature of safety profile of this agent. However, more extensive data from prospective clinical trials evaluating the safety and efficacy of sorafenib in patients with compromised liver function would be ideally warranted. Recent data from the ongoing Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib (GIDEON) registry, an international non-interventional study involved in the collection of safety and clinical data concerning the treatment of patients suffering from Hepatocellular Carcinoma (HCC) may provide a clearer profile of risk and benefit in patients treated with sorafenib outside the clinical trial scenario.

The potential of sorafenib in advanced disease can also be extrapolated to studies in patients who will have or have already undergone resection, ablation, chemoembolization, or liver transplantation, wherein, sorafenib mediated neoadjuvant treatment could improve resection outcomes and increase surgical candidacy. Sorafenib additionally offers the possibility of bridging therapy for patients with HCC awaiting transplantation.

The success of sorafenib will definitely encourage the clinicians to proceed with other targeted therapies and their combinations in HCC, as well as to investigate the potential role of biomarkers predictive of tumor response, such as those of anti-angiogenic effect and tyrosine kinase inhibition.[49,50]

In conclusion, sorafenib, by virtue of demonstrating a survival benefit via favorable effects on both proliferation and angiogenesis, definitely harbors the potential to make a significant contribution in the management of patients with advanced, inoperable HCC. However, additional studies are awaited to better define which subsets of patients will exactly benefit from sorafenib therapy and the meticulous role of this agent as an adjunctive therapy in combination with other treatment modalities.

Thus, even in the midst of some considerable hype, sorafenib has ushered in an era of hope for patients with unresectable HCC and the flurry of activities surrounding the molecule is currently in an exciting stage of development.

REFERENCES

1. Wands JR, Blum HE. Primary hepatocellular carcinoma. N Engl J Med 1991; 325: 729–731.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74–108.
3. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001; 94: 153–156.
4. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003; 362: 1907–1917.
5. Bosch FX, Ribes J, Cleries R, Diaz M. Epidemiology of hepatocellular carcinoma. Clin Liver Dis 2005; 9: 191–211.
6. Abdel-Hamid NM. Recent insights on risk factors of hepatocellular carcinoma. World J Hepatol 2009; 1: 3-7.
7. Pisani P, Parkin DM, Ferlay J. Estimates of the worldwide mortality from eighteen major cancers in 1985. Implications for prevention and projections of future burden. Int J Cancer 1993; 55: 891–893.
8. Bosch FX. Global epidemiology of hepatocellular carcinoma. In: Okuda K, Tabor E, editors. Liver Cancer. New York: Churchill Livingstone; 1997.p. 13–27.
9. Annual Report 1987. National Cancer Registry Programme. New Delhi, Indian Council of Medical Research, 1990.
10. Jayant K, Rao RS, Nene BM, Dale PS. Rural Cancer Registry at Barshi- Report 1988-92. Barshi, Rural Cancer Registry, 1994.
11. Sarin SK, Thakur V, Guptan RK, Saigal S, Malhotra V, Thyagarajan SP, et al. Profile of hepatocellular carcinoma in India: an insight into the possible etiologic associations. J Gastroenterol Hepatol 2001; 16: 666–673.
12. Durga R, Muralikrishna P. Viral markers in hepatocellular carcinoma. Ind J Gastroenterol 1994; 13: A57.
13. Sundaram C, Reddy CRRM, Venkataramana G, Benerjea S, Venkatratnam G, Swarnakumari G, et al. Hepatitis B surface antigen, hepatocellular carcinoma and cirrhosis in South India-an autopsy study. Indian J Pathol Microbiol 1990; 33: 334–338.
14. Kumar A, Sreenivas DV, Nagarjuna YR. Hepatocellular carcinoma. The Indian scenario. Ind J Gastroenterol 1995; 14: A95.
15. Kar P, Budhiraja S, Narang A, Das BC, Panda SK, Chakravorty A. Comparative evaluation of serology and polymerase chain reaction for hepatitis C viral infection in liver diseases. Ind J Gastroenterol 1997; 16: 118–119.
16. Chenivesse X, Franco D, Brechot C. MDR1 (multidrug resistance) gene expression in human primary liver cancer and cirrhosis. J Hepatol 1993; 18: 168-172.
17. Jiang W, Lu Z, He Y, Diasio RB. Dihydropyrimidine dehydrogenase activity in hepatocellular carcinoma: Implication in 5-fluorouracil-based chemotherapy. Clin Cancer Res. 1997; 3: 395-399.
18. Soini Y, Virkajärvi N, Raunio H, Pääkkö P. Expression of P-glycoprotein in hepatocellular carcinoma: A potential marker of prognosis. J Clin Pathol 1996; 49: 470-473.
19. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003; 37: 429-442.
20. Iyer R, Fetterly G, Lugade A, Thanavala Y. Sorafenib: a clinical and pharmacologic review. Expert Opinion on Pharmacotherapy 2010; 11: 1943-1955.
21. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390.
22. Chang YS, Adnane J, Trail PA, Levy J, Henderson A, Xue D, et al. Sorafenib (BAY 43-9006) inhibits tumor growth and vascularization and induces tumor apoptosis and hypoxia in RCC xenograft models. Cancer Chemother Pharmacol 2007; 59: 561-574.
23. Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther 2008; 7: 3129-3140.
24. Scanga A, Kowdley K. Sorafenib: A glimmer of hope for unresectable hepatocellular carcinoma? Hepatology 2009; 49: 332-334.
25. Awada A, Hendlisz A, Gil T, Bartholomeus S, Mano M, de Valeriola D, et al. Phase I safety and pharmacokinetics of BAY 43-9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumours. Br J Cancer 2005; 92: 1855-1861.
26. http://www.univgraph.com/bayer/inserts/sorafenib.pdf.
27. Semela D, Dufour JF. Angiogenesis and hepatocellular carcinoma. J Hepatol 2004; 41: 864–880.
28. Schmidt CM, McKillop IH, Cahill PA, Sitzmann JV. Increased MAPK expression and activity in primary human hepatocellular carcinoma. Biochem Biophys Res Commun 1997; 236: 54–58.
29. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004; 64: 7099–7109.

30. Carlomagno F, Anaganti S, Guida T, Salvatore G, Troncone G, Wilhelm SM, et al. BAY 43-9006 inhibition of oncogenic RET mutants. J Natl Cancer Inst 2006; 98: 326–334.
31. Rahmani M, Davis EM, Bauer C, Dent P, Grant S. Apoptosis induced by the kinase inhibitor BAY 43-9006 in human leukemia cells involves down-regulation of Mcl-1 through inhibition of translation. J Biol Chem 2005; 280: 35217–35227.
32. Yu C, Bruzek LM, Meng XW, Gores GJ, Carter CA, Kaufmann SH, et al. The role of Mcl-1 downregulation in the proapoptotic activity of the multikinase inhibitor BAY 43-9006. Oncogene 2005; 24: 6861–6869.
33. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007; 356: 125-134.
34. Elser C, Siu LL, Winquist E, Agulnik M, Pond GR, Chin SF, et al. Phase II trial of sorafenib in patients with recurrent or metastatic squamous cell carcinoma of the head and neck or nasopharyngeal carcinoma. J Clin Oncol 2007; 25: 3766-3773.
35. Adjei AA, Molina JR, Mandrekar SJ, Marks R, Reid JR, Croghan G, et al. Phase I trial of sorafenib in combination with gefitinib in patients with refractory or recurrent non-small cell lung cancer. Clin Cancer Res 2007; 13: 2684-2691.
36. Meier F, Busch S, Lasithiotakis K, Kulms D, Garbe C, Maczey E, et al. Combined targeting of MAPK and AKT signalling pathways is a promising strategy for melanoma treatment . Br J Dermatol 2007; 156: 1204-1213.
37. Schneider BP, Sledge GW Jr. Drug insight: VEGF as a therapeutic target for breast cancer. Nat Clin Pract Oncol 2007; 4: 181-189.
38. Siu LL, Awada A, Takimoto CH, Piccart M, Schwartz B, Giannaris T, et al. Phase I trial of sorafenib and gemcitabine in advanced solid tumors with an expanded cohort in advanced pancreatic cancer. Clin Cancer Res 2006; 12: 144-151.
39. Liu L, Cao Y, Chen C, Zhang X, McNabola A, Wilkie D, et al. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res 2006; 66: 11851-11858.
40. Strumberg D. Preclinical and clinical development of the oral multikinase inhibitor sorafenib in cancer treatment. Drugs Today (Barc) 2005; 41: 773-784.
41. Abou-Alfa GK, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006; 24: 4293-4300.
42. Lopez PM, Villanueva A, Llovet JM. Systematic review: Evidence-based management of hepatocellular carcinoma–an updated analysis of randomized controlled trials. Aliment Pharmacol Ther 2006; 23: 1535-1547.
43. Yeo W, Mok TS, Zee B, Leung TW, Lai PB, Lau WY, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. J Natl Cancer Inst 2005; 97: 1532-1538.
44. Gomaa AI, Khan SA, Toledano MB, Waked I, Taylor-Robinson SD, et al. Hepatocellular carcinoma: Epidemiology, risk factors and pathogenesis. World J Gastroenterol 2008; 14: 4300-4308.
45. World Health Organization: Hepatitis B. Geneva, Switzerland, World Health Organization, Department of Communicable Diseases Surveillance and Response, 2002.
46. Cheng A, Kang Y, Chen Z, Tsao C, Qin S, Kim J, et al. Randomized phase III trial of sorafenib versus placebo in Asian patients with advanced hepatocellular carcinoma. J Clin Oncol 2008; 26: 215s.
47. Abou-Alfa GK, Amadori D, Santoro A, Figer A, De Greve J, Lathia C, et al. Is sorafenib (S) safe and effective in patients (pts) with hepatocellular carcinoma (HCC) and Child-Pugh B (CBP) cirrhosis? J Clin Oncol 2008; 26: 217s.
48. Yau T, Chan P, Ng K, Chok K, Fan ST, Poon R, et al. Efficacy and tolerability of single agent sorafenib in poor risk advanced hepatocellular carcinoma patients. J Clin Oncol 2008; 26: 656s.
49. DePrimo SE, Cheng A, Lanzalone S, Lechuga MJ, Harmon CS, Lin X. et al. Circulating biomarkers of sunitinib in patients with unresectable hepatocellular carcinoma (HCC): Analysis of correlations with outcome and tumor imaging parameters. J Clin Oncol 2008; 26: 236s.
50. Zhu AX, Sahani DV, di Tomaso E, Duda DG, Catalano OA, Ancukiewicz M, et al. Sunitinib monotherapy in patients with advanced hepatocellular carcinoma (HCC): Insights from a multidisciplinary phase II study. J Clin Oncol 2008; 26: 218.