Systemic Therapy of Hepatocellular Carcinoma

Current and Promising

Aparna Kalyan, MD[a,b], Halla Nimeiri, MD[a,b], Laura Kulik, MD[b,c,*]

KEYWORDS

• Hepatocellular carcinoma • Systemic therapy • Targeted agents

KEY POINTS

- Sorafeninb is the only approved systemic therapy for hepatocellular carcinoma (HCC).
- Side effects of sorafenib need to be closely monitored.
- Newer agents have failed to show a benefit over sorafenib.
- A personalized approach to HCC to capitalize and inhibit the genes driving hepatocarcinognesis is needed.

SYSTEMIC THERAPY FOR HEPATOCELLULAR CARCINOMA

The incidence of hepatocellular carcinoma (HCC) continues to increase and although there have been advancements in therapy, HCC has become the second leading cause of cancer-related mortality worldwide.[1] Treatment of HCC is confounded by the competing risk of morbidity and mortality imposed by underlying cirrhosis that is present in nearly 90% of patients with HCC. The treatment of HCC must balance efficacy from an oncologic standpoint with the ability of a diseased liver to tolerate the therapy.

Historically, cytotoxic chemotherapeutic agents have been poorly tolerated in HCC and have not demonstrated a reproducible benefit of improved overall survival (OS).[2] The approval of sorafenib in 2006 ushered in the era of targeted agents.[3] However, the redundant molecular pathways in hepatocarcinogenesis that eventually render the inhibition of the targeted molecular pathway inadequate to control tumor growth have

Disclosure: Dr. Kulik is on the Bayer Advisory Board, Blue Print Advisory Board and is Speaker for Abbvie & Gilead.

[a] Northwestern Medicine Developmental Therapeutics Institute (NMDTI), Chicago, IL, USA; [b] Division of Hematology and Oncology, Robert H. Lurie Medical Research Center, Room 5-121, 303 East Superior, Chicago, IL 60611, USA; [c] Division of Hepatology and Gastroenterology, Northwestern University, 676 North St Clair, 19th Floor, Chicago, IL 60611, USA

* Corresponding author. Division of Gastroenterology and Hepatology, Department of Medicine, Northwestern University, 676 North St Clair, 19th Floor, Chicago, IL 60611.
E-mail address: lkulik@nm.org

Clin Liver Dis 19 (2015) 421–432
http://dx.doi.org/10.1016/j.cld.2015.01.009 **liver.theclinics.com**
1089-3261/15/$ – see front matter

limited the sustained efficacy of small molecules. Chronic inflammation leading to fibrosis is a key contributor to hepatocarcinogenesis. As the hepatocytes attempt to regenerate under the ongoing insult of viral hepatitis, alcohol, or oxidative stress related to fatty liver disease, DNA mutations accumulate and lead to the development of cancer. Additionally, fibrogenesis itself contributes to the development of cancer via promotion of angiogenesis and antiapoptotic factors.[4,5] This article reviews systemic therapy for HCC.

SORAFENIB

Sorafenib remains the only approved systemic therapy available for unresectable HCC. Several questions remain unanswered. The vast majority of patients enrolled in the 2 randomized controlled trials that demonstrated improved OS and prolonged time to progression (TTP) associated with sorafenib compared with placebo were Child–Turcotte–Pugh (CTP) class A with a performance status of 0 or 1.[6,7] The interim analysis of the Global Investigation Of Therapeutic Decision In Hepatocellular Carcinoma And Of Its Treatment With sorafenib (GIDEON), a prospective observational trial of patients treated with sorafenib in real-life clinical practice, highlighted that OS is influenced by CTP status: CTP-A 10.3 versus CTP-B 4.8 months. TTP was similar between CTP-A and CTP-B.[8] Additionally, the development of worsening hepatic function with longer duration of sorafenib has been reported in CTP-B compared with CTP-A.[9] Whether this decline in liver function is attributable to the underlying liver disease itself or related to drug exposure is not known. The final analysis of GIDEON was presented at the American Society for Clinical Oncology (ASCO) meeting in 2013.[10] A total of 3202 patients were evaluated. There was no significant difference in drug-related side effects across CTP classes; however, serious adverse events were more evident in the CTP-B subgroup. Similar to the results of the interim analysis, OS was influence by CTP classification: median OS in CTP-A was 13.6 months (95% CI, 12.8–14.7) and in CTP-B it was 5.2 months (95% CI, 4.6–6.3). The shortest OS was observed in those with CTP-B (score 9) at 3.7 months. TTP was not different according to CTP class: in CTP-A it was 4.7 months (95% CI, 4.3–5.2) and in CTP-B it was 4.4 months (95% CI, 3.5–5.5). The safety and efficacy of sorafenib in CTP-B patients is being examined in an ongoing randomized, controlled trial (RCT), the B Child Patient–Optimization Of Sorafenib Treatment (BOOST) trial (NCT01405573).

The approved dose for sorafenib is 400 mg bid. Dose reductions for side effects, including hand–foot skin reaction (HFSR; **Table 1**), hypertension, diarrhea, and fatigue are often needed in the management of patients on sorafenib. Alternatively, the strategy of initiating sorafenib at 200 bid and titrating up as tolerability allows is often used in clinical practice. Insight into the correlation between drug dosing and duration with OS is limited to a retrospective analysis by Iavarone and colleagues.[9] All patients were started on full-dose sorafenib. However, those patients who required a dose reduction had an overall longer duration of therapy compared with those treated with full dose (6.8 vs 3 months, respectively) and the OS was 21.6 months among those on reduced dose compared with 9.6 months in those continued on full dose. Owing to the retrospective nature of these data, conclusions and therefore recommendations regarding the best dose regimen of sorafenib cannot be drawn. Some experts have hypothesized that the observed improved outcomes with lesser doses of sorafenib may be owing to differences in pharmacodynamics. The suggestion is that in those developing side effects requiring dose reductions, this is an indication of higher kinase inhibition in vivo, compared with those able to tolerate full dose.[11] In line with this idea, side effects such as HFSR have been reported to be associated with a TTP compared with