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Novel Therapies to Increase Durable Remission Rates for T-Cell Lymphoma

BY VALERIE NEFF NEWITT

"I am my mother's son," said a reflective Samuel Ng, MD, PhD, Instructor of Medicine at Harvard Medical School, as well as Attending Physician in the Lymphoma Program of the Division of Hematologic Malignancies and a researcher exploring the biology of T-cell lymphomas at Dana-Farber Cancer Institute, Boston.

Though he was born in Boston, Ng moved with his family to Arizona when he was 5. "My mom took a job in Phoenix running a senior citizen center. She organized meals for the elderly, helped them to find essential services, drove them to medical appointments, and more. Every time we went out to a restaurant someone would come up and thank her for something she'd done. It left a big impression on me; it made me want to help people when I can."

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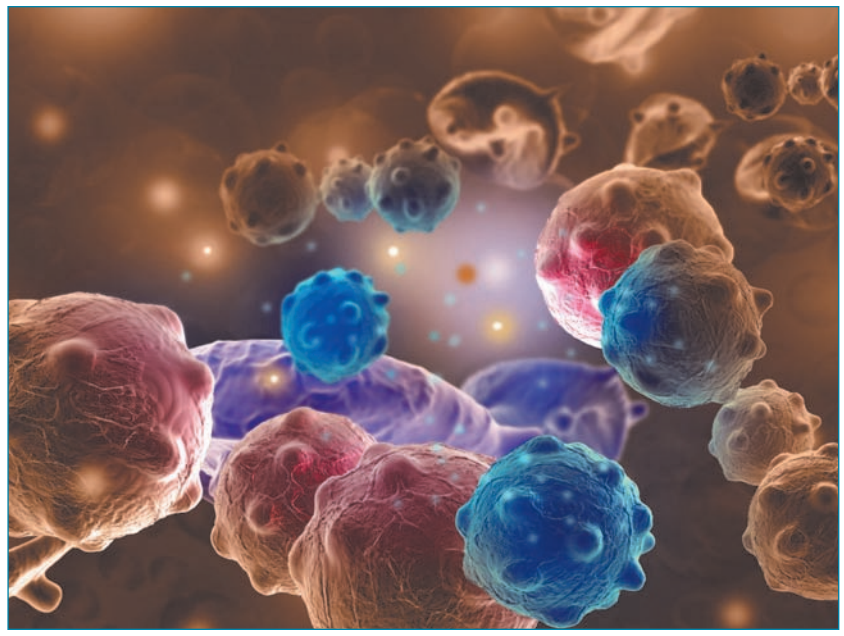

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Lenvatinib vs. Sorafenib as First-Line Treatment for Unresectable HCC

BY RICHARD SIMONEAUX

Hepatocellular carcinoma (HCC) is the most common form of liver cancer, often affecting those that have underlying chronic liver inflammation. Every year, globally, more than 700,000 people are diagnosed with HCC and, additionally, more than 600,000 die from it. For patients with unresectable HCC, there are few efficacious treatment options.

Recently, results were published from an international, open-label, phase III non-inferiority trial (NCT01761266) that compared the use of lenvatinib versus sorafenib in treatment-naïve HCC patients with unresectable disease (*Lancet* 2018;391:1163-1173).

CME Article

One of the investigators on this study was Richard S. Finn, MD, Assistant Professor of Medicine at the Geffen School of Medicine at UCLA. "In this study, lenvatinib was evaluated as a first-line therapy versus sorafenib, at the time, the only systemic therapy to have shown efficacy relative to placebo in patients with advanced HCC," Finn noted. "As a

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One Step Closer to Personalized Medicine for Leukemia

Scientists at the University of Birmingham in the U.K. have revealed the roles that different types of gene mutations play in causing blood cancers in a study that was the culmination of a decade's research.

The findings of the team, led by Constanze Bonifer, PhD, and Peter Cockerill, PhD, both of the University of Birmingham's Institute of Cancer and Genomic Studies, mean clinicians are now one step closer to being able to provide tailored and targeted treatment specific to individual patients—increasing their chances of survival.

The team, funded by blood cancer research charity Bloodwise, has spent the last 10 years carrying out a global analysis of the cells of patients diagnosed with acute myeloid leukemia (AML), the results of which have been published in *Nature Genetics* (2018; doi:10.1038/s41588-018-0270-1).

Targeting Mutations

AML is an aggressive cancer of the myeloid cells, which normally function to fight bacterial infections and eliminate parasites from the body. By picking apart the mutated cells in AML patients and gathering big data on each of them, the researchers were able to study the basic building blocks that control the production of these abnormal cells.

This step-by-step process, carried out in collaboration with Mike Griffiths and his team at the West Midlands Regional Genetics Laboratory at Birmingham Women's and Children's NHS Foundation Trust, identified the main trigger points where critical mutations feed through to other genes that control the cells' identity and behavior.

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result of the findings obtained in this non-inferiority trial, on Aug. 16, 2018, the FDA approved the use of lenvatinib as a first-line therapy for patients with unresectable HCC."

Hepatocellular Carcinoma

As previously stated, HCC is the most common form of primary hepatic malignancy, often arising in individuals that have chronically inflamed livers. The majority of the HCC cases worldwide occur in regions where hepatitis B is endemic, such as Asia and sub-Saharan Africa; however, hepatitis C is also a major risk factor for HCC. The increased rates of hepatitis C in the U.S. are often cited as one of the drivers for the rising incidence of HCC in this country. Aside from viral hepatitis, which accounts for roughly 75 percent of HCC cases, other common risk factors for this disease include chronic alcoholism (resulting in cirrhosis), aflatoxin exposure, type 2 diabetes and fatty liver disease, and hemochromatosis.

For patients with unresectable HCC, there are very few effective treatment options. In November 2007, the FDA approved the use of the first systemic drug, sorafenib, for the treatment of unresectable HCC (*N Engl J Med* 2008;359:378-390). This compound is a multi-kinase inhibitor, inhibiting both tyrosine and serine/threonine kinases. Mechanistically, sorafenib showed inhibition of angiogenesis and tumor cell proliferation, as well as increased tumor cell apoptosis in preclinical studies (*Cancer Res* 2006;66:11851-11858).

For HCC patients not progressing on first-line sorafenib therapy, there have been two fairly recent approvals for second-line therapies. In April 2017, the FDA granted approval to regorafenib as the first agent to improve survival in the second-line treatment for HCC patients having prior sorafenib therapy. This approval was based on the results from a phase III clinical trial (*Lancet* 2017;389:56-66, NCT01774344) that compared regorafenib and placebo in sorafenib-treated unresectable HCC patients. Regorafenib, like sorafenib, is a multi-kinase inhibitor with a generally similar mechanism of action.

In September 2017, the FDA granted accelerated approval for the use of the checkpoint inhibitor nivolumab in unresectable HCC patients who had received prior sorafenib therapy. In their press announcement, the FDA cited results from a 154-person subgroup of the phase III CheckMate 040 study that demonstrated a response rate of 14.8 percent and a duration of response of over 16 months for those that respond (*Lancet* 2017;389:2492-2502, NCT01658878).

Lenvatinib

Lenvatinib is a multi-kinase inhibitor that has been approved for a number of different malignancies. Mechanistically, this compound targets several different tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR, isoforms 1, 2, and 3); fibroblast growth factor receptor (FGFR, isoforms 1, 2, 3, and 4); proto-oncogene c-KIT; platelet-derived growth factor-α (PDGF); and RET proto-oncogene.

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The first indication for which this inhibitor received FDA approval was for the treatment of radioactive iodine-refractory progressive differentiated thyroid cancer (February 2015). Subsequently, in May 2016, this compound received FDA approval in combination with the mTOR inhibitor everolimus for the treatment of advanced renal cell carcinoma patients who had received one prior anti-angiogenic therapy.

REFLECT Trial

REFLECT was a randomized, phase III, open-label non-inferiority study that was performed at 154 different treatment centers in 20 different countries, including those in Europe, North America, and the Asia-Pacific region. Patients were randomized in a 1:1 manner to either the lenvatinib or sorafenib groups.

Among the key inclusion criteria were the following:

- histologically, cytologically, or clinically confirmed unresectable HCC using American Association for the Study of Liver Diseases criteria;
- one or more measurable liver lesions using modified Response Evaluation Criteria in Solid Tumors (mRECIST);
- Barcelona Clinic Liver Cancer stage B or C disease; Child-Pugh class A;
- ECOG performance status score of 0 or 1;
- controlled blood pressure (≤150/90 mm Hg); and
- adequate bone marrow, hematologic, hepatic, pancreatic, and renal function.

Patients were excluded from participation in this study if they had any of the following: prior systemic therapy for HCC; 50 percent or higher liver occupation; and obvious bile duct or main portal vein invasion.

"Patients could participate in this study if they had target lesions that had been previously treated with radiotherapy or locoregional therapy that subsequently showed radiographic evidence of disease progression," Finn stated.

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Learning Objectives for This Month's CME Activity: After participating in this CME activity, readers should be better able to: 1. Appraise the results of the Phase 3 Evaluation of lenvatinib vs. sorafenib as first-line treatment for unresectable hepatocellular carcinoma (HCC). 2. Propose encouraging second-line treatments for HCC patients having prior sorafenib therapy.

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Methodology

The study's primary endpoint, overall survival (OS), was defined as the time between randomization and the date of death from any cause. "Patients lost to follow-up were censored at the last date they were known to be alive, while those who remained alive were censored at the time of data cutoff (Nov. 13, 2016)," Finn explained.

Among the secondary endpoints were progression-free survival (PFS), time to progression (TTP), objective response rate (ORR), and quality-of-life measurements. "Efficacy measurements were performed using all patients randomized in this study," Finn stated.

Safety, as assessed by adverse events (AEs), were graded using the NCI Common Terminology Criteria for Adverse Events Version 4.0. "Safety evaluations were performed using the safety analysis set of patients (i.e., all who received at least one dose of study treatment)," Finn clarified.

Patients receiving oral lenvatinib were dosed differently according to their weights. Those weighing 60 kg or more received 12 mg/day, while those under 60 kg received 8 mg/day in 28-day treatment cycles. Patients randomized to the sorafenib arm were dosed orally at 400 mg BID in 28-day cycles. Regarding dose interruption/modification, Finn stated, "Dose interruptions followed by reductions for lenvatinib-related toxicities were permitted, while modifications to sorafenib doses were implemented using the prescribing information for each region, with all sorafenib participants receiving 400 mg BID orally as an initiating dose."

Tumors were assessed by local investigators with mRECIST using CT or MRI via a triphasic scanning technique. These assessments were performed every 8 weeks, irrespective of dose interruptions, until radiological disease progression. "Patients discontinuing study treatment without disease progression had tumor assessments every 8 weeks or until disease progression or the start of another anticancer therapy," Finn added.

Results

From March 1, 2013, to July 30, 2015, 1,492 patients were recruited for enrollment in this study, and of these, 954 patients from 20 countries were deemed eligible and randomized to either the lenvatinib (n=478) or sorafenib (n=476) arms. "Baseline characteristics between the two groups were generally similar, with the exception of α-fetoprotein concentration (higher in the lenvatinib group) and hepatitis C etiology (higher in the sorafenib group)," Finn noted.

At the date of data cutoff, there were 701 deaths and the median follow-up times were 27.7 months and 27.2 months for the lenvatinib and sorafenib arms, respectively.

The median OS was 13.6 months (95% CI: 12.1-14.9 months) for the lenvatinib arm, and 12.3 months (95% CI: 10.4-13.9) for the sorafenib arm, affording a HR of 0.92 (95% CI: 0.79-1.06). "In terms of OS," Finn observed, "lenvatinib did not show superiority. However, it did show non-inferiority (the non-inferiority margin was set at 1.08).

"The effect of lenvatinib and sorafenib on median OS was consistent across subgroups based on baseline characteristics. However, although baseline α-fetoprotein concentration was not pre-specified for patient stratification, those having baseline α-fetoprotein concentrations <200 ng/mL had longer OS than those with α-fetoprotein concentrations of ≥200 ng/mL. This trend was observed in both treatment arms; interestingly, more patients in the sorafenib arm had lower baseline α-fetoprotein levels (i.e., <200 ng/mL) compared with the lenvatinib arm, and the benefit was greater with lenvatinib in the patients with a higher baseline AFP (≥200 ng/mL)."

Assessment by local investigators using mRECIST provided median PFS values of 7.4 months (95% CI: 6.9-8.8 months) and 3.7 months (95% CI: 3.6-4.6 months) for the lenvatinib and sorafenib arms, respectively, providing a HR of 0.66 (95% CI: 0.57-0.77; p<0.0001). The median TTP was 8.9 months (95% CI: 7.4-9.2 months) for the lenvatinib patients and 3.7 months (95% CI: 3.6-5.4 months) for the sorafenib participants, which gave a HR of 0.63 (95% CI: 0.53-0.73; p<0.0001).

The ORR for the lenvatinib patients (i.e., those having partial or complete responses) was 24.1 percent (95% CI: 20.2-27.9%), while for the sorafenib patients, the value was 9.2 percent (95% CI: 6.6-11.8%), giving an odds ratio of 3.13 (95% CI: 2.15-4.56; p<0.0001).

Discussion

"In this study, statistically significant improvements were noted for lenvatinib compared to sorafenib for all secondary efficacy endpoints (e.g., PFS, TTP, and ORR) as determined by investigator tumor assessments based on mRECIST," Finn stated. "These improvements were consistent across all predefined subgroups."

> "This study marks the first time in a decade that a first-line therapy has displayed non-inferiority to sorafenib in treating hepatocellular carcinoma."

When questioned about the frequency of dose interruptions and reductions in this study, Finn replied, "Treatment-related treatment-emergent AEs led to lenvatinib interruption in 190 patients (40%), dose reduction in 176 patients (37%), and drug withdrawal in 42 patients (9%). For patients in the sorafenib arm, treatment-related treatment-emergent AEs led to drug interruption in 153 (32%), dose reduction in 181 (38%), and drug withdrawal in 34 patients (7%), respectively."

Discussing the frequency of AEs observed in this study, Finn stated, "When adjusted by patient-years, the rates for AEs were similar, 18.9 and 19.7 episodes per patient-year in the lenvatinib and sorafenib groups, respectively.

"Treatment-emergent AEs of grade 3 or higher occurred at similar rates in both study arms (lenvatinib-3.2 and sorafenib-3.3 episodes per patient-year)," he added.

The most frequently encountered treatment-emergent AEs in the lenvatinib patients were hypertension, diarrhea, decreased appetite, and decreased weight, while for those in the sorafenib arm, the most common treatment-emergent AEs were hand-foot syndrome, diarrhea, hypertension, and decreased appetite.

In summarizing these results, Finn stated, "Analysis for overall survival with predefined subgroups supports the robustness of the non-inferiority result. This study marks the first time in a decade that a first-line therapy has displayed non-inferiority to sorafenib in treating HCC, and this is supported by superiority of lenvatinib in regards to secondary endpoints." OT

Richard Simoneaux is a contributing writer.