HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Drugs in Development for Hepatocellular Carcinoma

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G&H What have been the most recent advances or changes in hepatocellular carcinoma drug development?

LR For approximately 10 years, the only drug available for advanced hepatocellular carcinoma (HCC) was sorafenib (Nexavar, Bayer), given as first-line treatment. Recently, regorafenib (Stivarga, Bayer) was approved for second-line treatment. In addition, nivolumab (Opdivo, Bristol-Myers Squibb) recently received accelerated approval in the United States for HCC patients who previously used sorafenib and will likely be approved elsewhere if its ongoing phase 3 study has positive results. Lenvatinib (Lenvima, Eisai) was approved very recently in the United States and in Japan for first-line treatment and will likely be approved soon in Europe and in other countries in the same setting. Also, cabozantinib (Cabometyx, Exelixis) will likely be approved for second- and third-line treatment soon; if so, this drug would be the first for third-line HCC treatment. Ramucirumab (Cyramza, Lilly) is also likely near approval and would be the first HCC drug for a biomarker-selected patient population (second-line treatment of patients with high baseline α-fetoprotein [AFP] values [≥400 ng/mL]). Thus, the landscape of HCC treatment is becoming more complex, and it will be important to refine the treatment algorithm for HCC patients.

G&H What are the most recent clinical trial data on nivolumab for the treatment of HCC?

LR At present, there are several studies on various programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors, but the most important phase 1 and 2 data come from the CheckMate 040 trial on the PD-1 inhibitor nivolumab. This study examined both patients who were previously treated with sorafenib and those who were not, as well as both patients with hepatitis B or C virus infection and those without the diseases. The median overall survival was 28.6 months with nivolumab as first-line treatment and approximately 15 months with the drug as second-line treatment. These results were impressive, although it is important to keep in mind that they are only phase 1 and 2 data, not phase 3 data.

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Similar results were recently published from the KEYNOTE-224 trial with the PD-1 inhibitor pembrolizumab (Keytruda, Merck) as second-line treatment. Median

overall survival was 12.9 months with the drug. The US Food and Drug Administration is currently reviewing an application for accelerated approval of pembrolizumab for second-line HCC treatment.

In addition, a phase 3 trial of nivolumab vs sorafenib as first-line HCC treatment and a phase 3 trial of pembrolizumab vs placebo as second-line treatment have recently completed patient enrollment. No data are available yet, so we will have to wait to find out whether the phase 3 results will confirm the promising phase 1 and 2 data. As previously mentioned, nivolumab recently received accelerated approval for second-line treatment in the United States, and if the phase 3 data are positive, the drug will likely be approved in other countries. Nivolumab is not yet approved in Europe because the European Medicines Agency did not consider the phase 1 and 2 data enough to approve the drug.

G&H What data have been reported recently on the use of lenvatinib for HCC treatment?

LR The multikinase inhibitor lenvatinib targets different types of vascular endothelial growth factor receptors (VEGFRs) and different types of fibroblast growth factor receptors, among other receptors. The drug was recently studied in an open-label, noninferiority, phase 3 study vs sorafenib as first-line treatment. According to the results, which were published this year, lenvatinib was noninferior to sorafenib in terms of overall survival. In addition, lenvatinib was superior to sorafenib in terms of progression-free survival. Adverse events were quite similar in the 2 treatment arms, other than a higher incidence of hypertension with lenvatinib and a higher incidence of skin toxicity with sorafenib. Quality of life was better with lenvatinib than with sorafenib for some of the items evaluated; however, for most of the evaluated items, quality of life was similar between the 2 treatment arms.

Considering that these results come from a phase 3 trial, lenvatinib will likely be approved soon for first-line treatment also in Europe and in other countries, following the approvals in the United States and in Japan, making it another treatment option for advanced HCC in many countries. Therefore, the treatment algorithm will need to be refined in terms of the sequence of treatment when lenvatinib is used for first-line therapy; in all of the second- and third-line trials to date, the enrolled patients were previously treated with sorafenib, not with lenvatinib.

As for the next steps with this drug, there is ongoing phase 1 research on the combination of lenvatinib and pembrolizumab for the treatment of HCC.

G&H What is the most recent research on the use of cabozantinib for HCC treatment?

LR Cabozantinib is an oral tyrosine kinase inhibitor of VEGFR, MET, and AXL, which are involved in HCC progression. This drug was studied first in a phase 2 trial and then in a phase 3 trial (the CELESTIAL trial) as second- and third-line treatment, the results of which were published this year.

In the CELESTIAL trial, patients had previously been treated with sorafenib, could have received up to 2 lines of treatment, and progressed after at least 1 of the lines. More than 700 patients were enrolled and randomized 2:1 to cabozantinib or placebo. Median overall survival was 10.2 months on cabozantinib and 8.0 months on placebo. In addition, median progression-free survival and the objective response rate were higher with cabozantinib compared to placebo (5.2 months vs 1.9 months and 4% vs <1%, respectively). Second-line patients (ie, patients treated only with prior sorafenib) also did better with cabozantinib compared to placebo; overall survival was approximately 11 months compared to 7 months, respectively. The tolerability and safety profile of the drug were acceptable; the main adverse events in the trial were typical of multikinase inhibitors (eg, hypertension, skin toxicity, fatigue).

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Cabozantinib will likely be approved for second- and third-line treatment of patients with HCC owing to the positive results from this large phase 3 trial. Future research might include investigating cabozantinib in combination with other oncology drugs or perhaps examining the drug in patients who have previously been treated with drugs other than sorafenib.

G&H What have studies recently reported regarding the use of ramucirumab for HCC treatment?

LR Ramucirumab is an intravenous monoclonal antibody against VEGFR2. The drug was examined in a phase 3 study (the REACH trial), which had negative results,

but the investigators were able to identify a preplanned subgroup of patients who benefited from the drug (patients with elevated baseline AFP levels). Thus, the phase 3 REACH-2 trial was conducted only in patients with high baseline AFP levels, and the data were recently presented at this year's American Society of Clinical Oncology meeting. The study participants, who had previously been treated with sorafenib, received either ramucirumab or placebo. The results demonstrated that patients with high baseline AFP levels did better with ramucirumab compared to placebo as second-line therapy; overall survival was 8.5 months on ramucirumab vs 7.3 months on placebo, and median progression-free survival was 2.8 months vs 1.6 months, respectively. The drug was very well tolerated, with the most relevant adverse event being hypertension. I expect that this drug will be approved for second-line treatment of the specific subgroup of HCC patients who have high AFP levels. In the future, studies may examine ramucirumab in combination with other drugs.

G&H Are there any other promising HCC drugs in development?

LR There are many drugs in phase 1 and 2 development, as well as a number of promising drugs further along in development, in phase 3 trials. Most of the ongoing phase 3 trials involve PD-1 or PD-L1 inhibitors as monotherapy or in combination with other agents for first-line treatment. Also, phase 1 and 2 trials are evaluating PD-1 or PD-L1 inhibitors as monotherapy or in combination for second- and third-line treatment. Examples of combinations undergoing evaluation in phase 3 trials for first-line treatment include durvalumab (Imfinzi, AstraZeneca) plus tremelimumab, and atezolizumab (Tecentriq, Genentech) plus bevacizumab. Generally speaking, PD-1 and PD-L1 inhibitors have shown promising early data that need to be confirmed in large phase 3 trials.

G&H Overall, what are the most significant challenges in HCC drug development?

LR The biggest challenge is that up to 80% to 90% of patients with HCC also have liver cirrhosis, so 2 diseases have to be managed, which has important implications in terms of toxicity. Also, many HCC patients are diagnosed at an advanced stage when treatment options are limited. Thus, it is important to diagnose patients at an early or intermediate stage. Nevertheless, it can still be challenging to determine the appropriate time to switch patients with early- or intermediate-stage HCC that is progressing from local regional treatment to systemic therapy. If patients have been treated with local regional treatments many times, their liver may be decompensated by the time systemic treatment is an option, which means that some patients cannot receive the drugs discussed above or the patients may tolerate the drugs badly because their liver function is not well preserved.

In addition, it is not possible to predict the activity of these new drugs using biomarkers (except for ramucirumab), so in the near future, multiple HCC drugs will likely be available but it will be difficult to decide which patients should be treated with which drugs. Further research is needed to address this challenge.

Finally, the evaluation of treatment response is another challenge, as the criteria can vary. Thus, research is currently underway examining the different types of response criteria.

Dr Rimassa has served in a consulting or advisory role for Exelixis, Ipsen (which markets cabozantinib in Europe), Lilly, Bayer, and AstraZeneca.

Suggested Reading

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