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HEALTH POLICY

Me-too drugs with limited benefits — the tale of regorafenib for HCC

Bishal Gyawali and Vinay Prasad

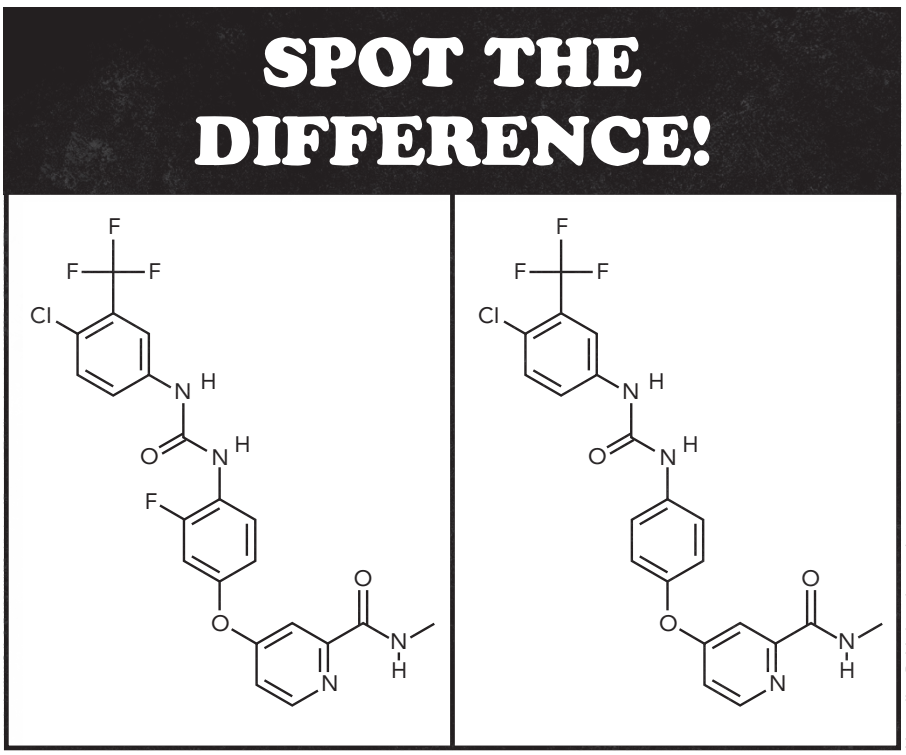
Regorafenib is only the second agent approved by the FDA for the treatment of patients with advanced-stage hepatocellular carcinoma. Herein, we discuss the evidence that led to the approval of this agent. Examination of this process reveals important challenges associated with drug regulation, relating to trial design, treatment toxicity, and real-world clinical benefit.

Refers to U.S. Food and Drug Administration. FDA expands approved use of Stivarga to treat liver cancer. *FDA* https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm555608.htm (2017)

On 27 April 2017, the FDA approved regorafenib as a second-line therapy for patients with locally advanced or metastatic hepatocellular carcinoma (HCC) with disease progression after sorafenib treatment[1]. Regorafenib is the first drug to be approved in this setting, and only the second molecular entity licensed for patients with HCC, the first being sorafenib — which received marketing authorization as a front-line therapy in 2007 (REF. 2). Before sorafenib, physicians typically used doxorubicin or other cytotoxic agents to treat this malignancy, with varying degrees of success; variable response rates were observed with these agents, ranging from 0% with paclitaxel, to 32% with doxorubicin[3].

The approval of sorafenib was based on the results of the pivotal phase III SHARP trial[4], which showed an improvement of the median overall survival duration compared with that observed with placebo (10.7 months versus 7.9 months; hazard ratio (HR) 0.69; $P<0.001$). The approval of regorafenib was also based on the results of a single phase III trial, the RESORCE study[5], in which patients with progressive disease after sorafenib therapy were randomly assigned to receive either regorafenib or placebo. Regorafenib improved median overall survival duration, from 7.8 months with placebo to 10.6 months (HR for regorafenib 0.63, $P<0.0001$). These data and the subsequent approval propelled regorafenib as a new treatment option for a historical unmet medical need; however, a closer examination of the approval process for this agent raises several key concerns about drug development and regulation.

First, even under ideal settings, the benefit of regorafenib is marginal. The efficacy of both sorafenib and regorafenib was determined in 'ideal' patient populations. In the SHARP trial[4], patients had limited comorbidities, an excellent performance status (PS; 92% of patients who received sorafenib had an ECOG PS of 0 or 1), and 95% in the sorafenib cohort had excellent liver function, classified as Child–Pugh category A. In the RESORCE trial[5], patients also had limited comorbidities, excellent PS (100% of patients had an ECOG PS of 0 or 1), and only patients with Child–Pugh A liver function were enrolled. Of note, the enrolment criteria of RESORCE[5] mandated the inclusion of only those patients who had tolerated ≥400 mg/day sorafenib for at least 20 of the last 28 days of treatment[5]. Given the high rates of dose reduction and/or treatment discontinuation with sorafenib in routine clinical settings[6], this criteria almost certainly enriched the study population for patients with the most favourable prognosis. Even in these ideal settings, only modest clinical benefit was achieved with each drug: the overall survival gain was 2.8 months in both studies, with similar hazard ratios. Of note, treatment with sorafenib also prolonged time-to-radiological progression (5.5 months versus 2.8 months; HR 0.58; $P<0.001$), but failed to improve time-to-symptomatic progression (4.1 months versus 4.9 months; HR 1.08; $P=0.77$).



Second, in 'real-world' settings, sorafenib underperforms these trial outcomes. Sanoff and colleagues[7] have analysed data from a population of patients with advanced-stage HCC who received treatment through Medicare; in the propensity score-matched effectiveness cohort, the median overall survival duration of patients receiving sorafenib ($n = 242$) was 3 months, only 1 month longer than that of patients not receiving any treatment ($n = 565$). Moreover, only 27% of the patients actually received sorafenib[7]. These findings highlight the vast differences between patients with cancer enrolled in clinical trials and those typically encountered in the clinic. In RESORCE[5], the median overall survival duration of patients receiving placebo — in the second-line setting — exceeded 7 months; such a long survival duration reflects the inclusion of only patients with an extremely favourable prognosis. Despite the characteristics of this patient group, the rates of grade 3, 4, and 5 toxicities were 46%, 4% and 2%, respectively, with regorafenib, versus 16%, 1%, and 1% with placebo. Thus, when regorafenib is used in routine clinical practice, the likelihood of this drug being less effective and more toxic than it was in the RESORCE trial is high — as is the case for sorafenib.

Third, these agents are associated with toxicity. Patients with HCC often have poor liver function; both sorafenib and regorafenib are known to contribute to liver dysfunction[4,5]. Indeed, liver dysfunction was one of the most common reasons (5%) for sorafenib discontinuation in the SHARP study[4], with dose reductions and interruptions occurring in 26% and 44% of patients receiving sorafenib, respectively, compared with 7% and 30% of patients receiving placebo. In the SHARP trial[4], the reported rates of serious hepatobiliary adverse events were 11% and 9% for sorafenib and placebo, respectively. A meta-analysis published this year[8] shows that sorafenib treatment is associated with an 86% increase in the risk of treatment-related serious adverse events (SAEs), and an 82% increase in the risk of fatal adverse events (FAEs) in patients with solid tumours, both significant compared with placebo or cytotoxic chemotherapy. In RESORCE[5], the rates of treatment-related SAEs and FAEs were 10% and 2%, respectively, compared with 3% and 1% with placebo. In the real-world setting, data on regorafenib use in patients with colorectal cancer suggests that SAEs are common (in a French study[9], 10% of patients had SAEs requiring hospitalization). For patients with HCC who have poor liver function, one can only expect these rates to be higher. Thus, many patients with HCC receiving first-line sorafenib treatment might not be able to tolerate regorafenib in the second-line setting. In addition, data from a patient registry in Taiwan[10] show that only 30% (46 of 149) of patients with progression of HCC after sorafenib treatment would meet the eligibility criteria for second-line therapy. Thus, regorafenib is only likely to be used by 8% of patients with HCC[7,10].

Clinical trial design is the fourth questionable aspect of this drug approval. Chemically, regorafenib and sorafenib differ by just one atom: a single hydrogen atom in sorafenib is substituted by a fluorine atom in regorafenib. Before the approval of regorafenib, some experts had advocated for the use of sorafenib after progression among patients who had tolerated first-line treatment with the drug[11], on the basis that this pan-tyrosine-kinase inhibitor would continue to exert antitumour effect[11]. RESORCE should, therefore, have contained a third arm, in which patients would have received second-line sorafenib. Given that regorafenib and sorafenib were associated with nearly identical extensions in survival duration, data derived from patients in this third arm would have been most informative. Whether regorafenib is truly superior to sorafenib in the second-line setting is important to ascertain, as the cost of treatment with regorafenib is 1.5-fold that of sorafenib, and the latter is much closer to generic manufacture (the estimated patent expiry dates are 2020 for sorafenib, and 2024 for regorafenib).

Examination of the approval of regorafenib by the FDA highlights several lessons that need to be learned. The first is that dissimilarities between patient populations in pivotal trials and real-world settings must be taken into account in approval decisions. The purpose of drug regulation is to permit the marketing of drugs that benefit patients. In the USA, strong preliminary evidence from a well-designed study[7] suggests that sorafenib has failed to do so. The RESORCE study is even less representative of real-world patient populations. In such situations, we favour granting accelerated approval conditional to validation in post-marketing studies of the efficacy of the drug in real-world patients, rather than granting full marketing authorization, because such authorizations seldom entail further efficacy commitments. The second lesson is related to drug similarities. When novel anticancer drugs bear incredible structural similarity to already available drugs, and experts have previously endorsed the off-label use of those 'parent' drugs in a particular setting, we wonder whether manufacturers have the obligation to show the new drug is superior: third-party comparative-effectiveness studies are essentially impossible, owing to the high prices of new drugs. Given the difference in price and market exclusivity period between regorafenib and sorafenib, this question is of broad relevance. For sure, some patients with HCC will benefit from treatment with regorafenib — how many and by how much more than is possible with sorafenib remains uncertain.

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Competing interests statement
The authors declare no competing interests.

ERRATUM

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In the illustration that accompanies this article, the structures of regorafenib and sorafenib were incorrectly drawn. In both structures, a double bond was omitted from the central phenyl ring so that it appeared as a 1,3-cyclohexadiene. The figure has been corrected in both the HTML and PDF versions of this News & Views.