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Commentary

Bridging the Gap Between Sorafinib Efficacy and Effectiveness in Advanced Hepatocellular Carcinoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

The issue of generalizability of clinical trial results has been a longstanding concern in adult oncology. The magnitude of benefit seen in the research setting is often not reproducible in practice, and toxicity is often greater in the general population. Several characteristics of trials create an environment for better outcomes in the research setting, including strict eligibility criteria for enrollment, specific guidelines for managing adverse events, training of investigators, and additional layers of patient monitoring beyond the treating clinician. Moreover, with only 2%–5% of adult patients participating in clinical trials, trial populations may not accurately represent the general population [1–3]. This is especially true for geriatric patients, a population that carries a disproportionately high cancer burden yet remains significantly underrepresented in clinical trials [4–6]. A National Cancer Institute study showed that although 61% of patients with cancer in the U.S. are ≥65 years old, only 32% of participants in phase II and III clinical trials are in this age group [4]. This discrepancy can affect the generalizability of clinical trial findings to older patients, particularly the Medicare population, in which more than 80% of beneficiaries are older than 65 years [7].

In this issue of ***The Oncologist***, Sanoff et al. report the results of an observational study evaluating the effectiveness of sorafenib in Medicare beneficiaries diagnosed with advanced hepatocellular carcinoma (HCC) between 2008 and 2011 [8]. Using the Surveillance, Epidemiology, and End Results (SEER) database, the authors found that of the 1,532 treatment-naïve patients evaluated, 27% received sorafenib and the remainder never received treatment for HCC. In the patients who received sorafenib, median overall survival (OS) from the time of filling the prescription was 3 months. In the comparative survival analysis of the 807 patients who survived at least 60 days from diagnosis, the median OS from the 60-day timepoint for sorafenib users versus untreated patients was 3 versus 2 months, respectively, a difference that was not statistically significant [8]. Notably, these OS statistics are significantly lower than those seen in the landmark Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, a randomized phase III trial of sorafenib versus placebo in patients with advanced HCC [9]. In that trial, the median OS in the sorafenib arm was 10.7 months, versus 7.9 months in the placebo arm.

A few critical strengths of the Sanoff et al. study should be acknowledged [8]. First, it offers insight into real-world outcomes with sorafenib based on the SEER database, which collects data from population-based cancer registries covering approximately 30% of the U.S. population [7]. This offers a more robust sample size and wider snapshot of outcomes in the general population compared with often-reported single-institution experiences. Second, many of the baseline characteristics of the study population in this report were similar to those in the SHARP trial [9], including predominantly male gender, Western population, and hepatitis C virus- and alcohol-related HCC (Table 1), thus providing a reasonable basis for comparability. Third, the authors prudently restricted the comparative analysis to patients who survived at least 60 days from diagnosis, a statistical approach that minimizes immortal time bias.

As the authors acknowledged, the finding of a 3-month survival with sorafenib in Medicare patients with advanced HCC should be interpreted with caveats. A key caution is that the study population included only patients who had no prior treatment for HCC. In the SHARP trial, nearly 50% of the patients had recurrent disease after prior surgery or liver-directed therapy [9]. This population, which is often on surveillance, tends to have a lower burden of disease and better prognosis than patients who require sorafenib up front. Indeed, Sanoff et al. reported a 9-month survival in the cohort of previously treated patients, which is much closer to that anticipated by the SHARP trial [8].

Second, although SEER data may reflect outcomes in real-world practice (effectiveness), they may underestimate the benefits of sorafenib in Medicare patients under ideal circumstances (efficacy). A key reason for this mismatch is that in the setting of limited treatment options, physicians often liberally apply the eligibility criteria that originally led to drug approval from the U.S. Food and Drug Administration. For example, whereas the SHARP trial required Child-Pugh (CP) A status for entry, patients with CP B cirrhosis often receive treatment in practice, and the latter subset has been shown to have a poor median OS of 5.2 months in the Global

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Table 1. Comparison of baseline characteristics in the Sanoff et al. [8] study and the SHARP trial [9]

	Sanoff et al. [8]		SHARP [9]	
Baseline characteristics	**Sorafenib**	**No treatment**	**Sorafenib**	**Placebo**
n	242	565	299	303
Age, years [median (Q1, Q3) or mean ± SD]	70 (64, 77)	74 (67, 82)	64.9 ± 11.2	66.3 ± 10.2
Male sex	186 (77)	380 (67)	260 (87)	264 (87)
Risk factor[a]				
HCV	76 (31)	174 (31)	87 (29)	82 (27)
Alcohol	31 (13)	86 (15)	79 (26)	80 (26)
HBV	26 (11)	42 (7)	56 (19)	55 (18)
Other	27 (11)	76 (13)	28 (9)	29 (10)
Tumor extent				
Multiple lesions, no vascular invasion	117 (48)	231 (41)		
Multiple lesions, with vascular invasion[b]	57 (24)	93 (16)	108 (36)	123 (41)
Extrahepatic disease	68 (28)	241 (43)	159 (53)	150 (50)
Prior treatment				
Surgery	0	0	57 (19)	62 (20)
Locoregional therapy	0	0	144 (48)	137 (49)
Systemic therapy	0	0	8 (3)	9 (3)

Data are presented as *n* (%) unless indicated otherwise.
[a]Sanoff et al.: patients with HCV, alcohol, HBV, and other risk factors; SHARP: patients with HCV only, alcohol only, HBV only, and other risk factors.
[b]SHARP trial indicates vascular invasion, but this category does not necessarily include multiple lesions.
Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; SHARP, Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol.

Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of Its Treatment with Sorafenib (GIDEON) study [10]. Given that the SEER database does not capture CP score, the current study may have included CP B patients, a population expected to have worse survival. Notably, the GIDEON study was a prospective, international, multicenter, noninterventional study of more than 3,000 patients with unresectable HCC treated with sorafenib that demonstrated a median OS for CP A patients of 13.6 months [10]. Thus, this global effectiveness study found outcomes comparable to those seen in the SHARP study [9]. Another eligibility criterion of the SHARP trial often not observed in practice is the requirement for histologic confirmation of HCC. Practice guidelines allow for radiographic diagnosis alone in the appropriate clinical setting [11], but intrahepatic cholangiocarcinoma can masquerade as HCC, and inadvertent inclusion of these patients may diminish the already modest benefits of sorafenib, which has demonstrated poor efficacy in intrahepatic cholangiocarcinoma [12]. Therefore, to delineate the true efficacy of sorafenib in the geriatric HCC population, researchers should consider a subgroup analysis of older patients in the SHARP trial or a prospective randomized trial dedicated to older patients.

Despite the caveats above, this study provides an opportunity for us to reflect on factors that may diminish the effectiveness of sorafenib in the Medicare population and offers critical insight for physicians prescribing sorafenib for older patients with HCC. First, comorbid cirrhosis is a major limiting factor in patients' ability to tolerate treatment for HCC, and older patients may have more advanced cirrhosis by virtue of living with the disease longer. Although severe hepatic dysfunction has not been associated with altered pharmacokinetics of sorafenib, it has been associated with increased risk of adverse events [13]. Second, clinicians may elect to reduce the dose of therapies for the Medicare population. In the Sanoff et al. study, at least 18% of patients started at a 50% dose reduction [8]. Additionally, older age is associated with poor adherence to oral chemotherapy regimens [14], which may be caused in part by poor tolerability, and this may lead to decreased drug exposure. Interestingly, data suggest that patient age does not significantly alter the pharmacokinetics of sorafenib [13, 15], despite it being 99.5% protein bound, poorly water soluble, and a strong substrate for CYP3A4.

A potential solution to improve the generalizability of cancer clinical trial results to the Medicare population is to increase enrollment of such patients in trials. The National Institutes of Health Act of 1993, which recommended inclusion of more geriatric patients in clinical research, and the creation of the International Society of Geriatric Oncology in 2000, which promotes the same mission, both stand as important landmarks in geriatric oncology. In practice, there are several patient, physician, and logistical barriers to trial enrollment for older and disabled patients. Patients may not meet eligibility as strict enrollment criteria often exclude those with comorbidities or inadequate organ function [16]. Moreover, patient preference for less aggressive care may also deter them from pursuing trial options. Physician factors may include assumptions regarding tolerability of or interest in experimental regimens in older patients [16, 17]. Logistical factors may include limited availability of caregivers, travel constraints, and financial concerns [18]. To address some of the unique challenges of older patients with cancer, several trials focused on this population are now underway. Although the number of

trials dedicated to the geriatric oncology population has increased steadily over time, further work is needed. One study showed that the number of clinical trials reporting specifically on older patients has increased, rising from 128 in 2001–2004 to 415 in 2011–2014 [19]. That study also showed that the proportion of phase III reports including a subgroup analysis of older patients enrolled has tripled (42% vs. 14%), although the proportion of phase III trials dedicated to older patients did not increase from 5% between the two time periods [19].

In summary, Sanoff et al.'s study highlights the difference between efficacy and effectiveness research and the importance of bridging the gap between them [8]. Strategies include actively enrolling more geriatric patients in clinical trials and designing prospective pragmatic trials with liberalized eligibility criteria suitable for older patients [20]. The latter provides an opportunity to enroll patients that reflect real-world practice, thereby improving reproducibility and generalizability. Ultimately, studies similar to that of Sanoff et al. that use large databases to assess outcomes of patients treated in routine practice provide crucial insights to help guide patient-clinician discussions and future clinical trial design.

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