Editorial

Clinical Trials As a Path Toward Equity

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The more things change, the more they remain the same: a cliche for sure; however, the specter of disparity and implications for health care delivery in the United States is on repeat. The paucity of justice, equity, and equality has been no more obvious than during our ongoing coronavirus 2019 (COVID-19) pandemic, as observed by many.

Racial and ethnic disparities and their effects on the delivery of health care, in particular cancer survival, have long been described. These inequities have been prevalent across the entire spectrum of cancer care, including prevention, early detection (screening), treatment, and survivorship care.[1] Disparities in gastrointestinal cancer risk and outcomes have been no exception. For example, California Cancer Registry data that included 161,820 patients who had colorectal cancer diagnosed between 2000 and 2013 indicated that cancer-specific mortality was significantly higher in Black men and women (36% and 34%, respectively) compared with non-Hispanic White patients, although adjustment for all covariables reduced the differences in women.[2] Stage at diagnosis was a significant factor explaining overall survival (OS) disparities. A National Cancer Database assessment of over 600.000 patients who had gastrointestinal cancers, including 62% with colon and rectal cancers, reported undertreatment of Black patients compared with White patients, represented by disproportionally low operative rates in Black patients and decreased survival.[3] African Americans also have the highest incidence of colorectal cancer among all US racial/ethnic groups, with a significant rate of rise for young Blacks.[4]

In this issue of *Cancer*, Snyder et al have assessed whether there were racial differences between Black and White patients who participated in the first-line therapy metastatic colorectal trial Cancer and Leukemia Group B (CALGB)/SWOG 80405 (ClinicalTrials.gov identifier NCT00265850), including OS, progression-free survival (PFS), and response to therapy as the primary objectives.[5] The trial compared the benefit of adding either cetuximab or bevacizumab to 5-fluorouracil, oxaliplatin, and leucovorin (FOLFOX) or 5-fluorouracil,irinotecan, and leucovorin (FOLFIRI) chemotherapy. This study is 1 of the most modern large, randomized trials for patients with metastatic colorectal cancer to date and as such represents the standard of care for patients with this disease.

As the authors report, Black patients with colorectal cancer have significantly higher incidence and mortality compared with White patients. Although mortality is decreasing in both Black and White individuals, the decline is principally seen in White patients. As referenced by the authors, previously published clinical trials have reported contradictory observations among trials that have analyzed differences between Black and White patients in the adjuvant setting, although overall it did appear that Black individuals had inferior outcomes compared with Whites. Limited data in the advanced disease setting (NCCTG N9741) showed no racial differences in the time to progression or OS.

CALGB/SWOG 80405 enrolled a total of 2334 patients, of whom 12% self-identified as Black and 81.5% self-identified as White. The final data set in this secondary analysis included 392 matched pairs of patients. Median OS and PFS did not significantly differ by race. In addition, there was no difference in response to therapy by race. Most toxicities did not differ by race, although Black patients had lower rates and lower odds of experiencing grade ≥3 fatigue. Those who underwent curative surgical resection for metastatic disease after initial chemotherapy were also similar in numbers. Increasingly, *KRAS* mutation status is recognized as a prognostic factor, and CALGB/SWOG 80405 similarly has demonstrated that patients with *KRAS* mutations have a lower survival probability than those with *KRAS* wild-type tumors. The study also noted no racial differences when patients were matched by *KRAS* status. The authors describe several limitations to their study as a secondary analysis of a propensity-matched cohort of patients. There were differences between the Black and White patients in performance status and palliative intention of treatment (vs neoadjuvant). They note a 3-month difference in the median overall survivorship between Black and White patients (26 vs 29 months, respectively); however, this did not reach significance, possibly because the study was underpowered to detect differences

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in survival by race. The *KRAS* analysis was also limited because 30% of the initial cohort of Black patients were missing *KRAS* status.

The authors conclude that, because patients received standardized treatment through their participation in this phase 3 randomized clinical trial, the racial disparities that have been observed in many other analyses are likely secondary to access to care and treatment delivery. Reducing variability in care is a potential significant advantage of patient access to clinical trials because the construct of most cancer treatment clinical trials defines rigorous testing, treatment parameters, toxicity monitoring, and ongoing assessment to optimally evaluate safety and efficacy outcomes. Adherence to cancer treatment guidelines provides yet another algorithm to reduce the variability of care and ensure that individuals are offered the most appropriate testing, treatment interventions, and follow-up to optimize outcomes. For patients with colon cancer in particular, analyses have demonstrated that adherence to guidelines can improve survival.[6,7]

The issue of reducing variability in oncologic care by encouraging enrollment in clinical trials and following recognized cancer treatment guidelines is confounded by a host of factors, most notably social determinants of health. For example, a recent SWOG Cancer Research Network analysis of over 41,000 patients with cancer who enrolled in 55 phase 3 and large phase 2 clinical trials showed that the clinical trial participants who lived in areas with the highest socioeconomic deprivation, compared with participants in the most affluent areas, had worse OS, PFS, and cancer-specific survival.[8] Another systematic review of published studies from 1970 through April 1, 2019, evaluated colorectal cancer and effects of social determinants of health, confirming that poverty, lack of education, immigration status, lack of social support, and social isolation are linked to colorectal cancer stage at diagnosis and survival.[9] Increasingly, race is viewed as a social construct and a proxy for poorer social determinants of health, which are more prevalent among communities of color. The American Cancer Society, in their recent blueprint for practice, research, and policy, has provided a construct to eliminate cancer-related disparities that provides recommendations to address structural inequities, institutional environments, living environments, risk factors, and the spectrum of cancer comorbidities and mortality.[1] The American Medical Association has approved a policy that replaces race with genetic ancestry or zip code to capture more fully the contribution of biologic differences or neighborhood deprivation on health disparities traditionally attributed to race.[10,11]

The low rate of participation in cancer clinical trials has been a longstanding dilemma that has not significantly reversed over the years. A recent landscape report assessing barriers to patient enrollment in therapeutic clinical trials for cancer estimated that the current overall rate of trial participation, including National Cancer Institute-sponsored and industry-sponsored therapeutic trials, was approximately 8%. That analysis also described significant demographic and socioeconomic disparities in trial enrollment. Of note were the significant racial and ethnic disparities, including marked underrepresentation of Black and American Indian/Alaska Native populations and those aged ≥70 years, particularly in US Food and Drug Administration-submitted cancer trials.[12] Even participation in a clinical trial does not guarantee equal treatment, as a trial standardizes the prescribed trial components and not the receipt of trial components; otherwise, we would not need to describe protocol deviations. Furthermore, treatment of comorbidities or adverse events may vary among participants, which can contribute to outcome heterogeneity.

This secondary analysis CALGB/SWOG 80405 demonstrates the potential that participation in a clinical trial provides a level of equity thus far elusive for the overall population of Black individuals with colorectal cancer. If we believe that cancer clinical trials represent a standard of care, then there will need to be dramatic changes in trial designs and clinical practice engagement with patients to ask individuals more consistently whether they would consider an available clinical trial at a minimum. The structure of a clinical trial (and cancer treatment guidelines) provides a mechanism for equity by integrating consistency in testing, treatment, and follow-up for all enrolled. What is lacking in trial design is the inclusion of factors beyond patient-reported outcomes addressing social determinants of health that not only clearly are detriments to trial enrollment but also can have profound consequences in outcomes, including survival. At a minimum, investigators need to include neighborhood-level deprivation using zip codes to more fully account for social determinants of health. The emphasis on shared decision making should provoke a conversation integrating social determinants of health and personal concerns and beliefs that might affect the delivery of care, whether on a trial or according to recognized standards of care, to better ensure access and equity.

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REFERENCES

1. Alcaraz KI, Wiedt TL, Daniels EC, Yabroff KR, Guerra CE, Wender RC. Understanding and addressing social determinants to advance cancer health equity in the United States: a blueprint for practice, research, and policy. *CA Cancer J Clin*. 2020;70:31-46. doi:10.3322/caac.21586
2. Ellis L, Canchola AJ, Spiegel D, Ladabaum U, Haile R, Gomez SL. Racial and ethnic disparities in cancer survival: the contribution of tumor, sociodemographic, institutional, and neighborhood characteristics. *J Clin Oncol*. 2018;36:25-33. doi:10.1200/JCO.2017.74.2049
3. Bliton JN, Parides M, Muscarella P, Papalezova KT, In H. Understanding racial disparities in gastrointestinal cancer outcomes: lack of surgery contributes to lower survival in African American patients. *Cancer Epidemiol Biomarkers Prev*. 2021;30:529-538. doi:10.1158/1055-9965.EPI-20-0950
4. Ashktorab H, Kupfer SS, Brim H, Carethers JM. Racial disparity in gastrointestinal cancer risk. *Gastroenterology*. 2017;153:910-923. doi:10.1053/j.gastro.2017.08.018
5. Snyder R, He J, Le-Rademacher J, et al. Racial differences in survival and response to therapy in patients with metastatic colorectal cancer: a secondary analysis of CALGB/SWOG 80405 (Alliance A151931). *Cancer*. 2021;127:3801-3808. doi:10.1002/cncr.33649
6. Boland GM, Chang GJ, Haynes AB, et al. Association between adherence to National Comprehensive Cancer Network treatment guidelines and improved survival in patients with colon cancer. *Cancer*. 2013;119:1593-601. doi:10.1002/cncr.27935
7. Chow Z, Gan T, Chen Q, Huang B, et al. Nonadherence to standard of care for locally advanced colon cancer as a contributory factor for high mortality rates in Kentucky. *J Am Coll Surg*. 2020;230:428-439. doi:10.1016/j.jamcollsurg.2019.12.041
8. Unger JM, Moseley AB, Cheung CK, et al. Persistent disparity: socioeconomic deprivation and cancer outcomes in patients treated in clinical trials. *J Clin Oncol*. 2021;39:1339-1348. doi:10.1200/JCO.20.02602
9. Coughlin SS. Social determinants of colorectal cancer risk, stage, and survival: a systematic review. *Int J Colorectal Dis*. 2020;35:985-995. doi:10.1007/s00384-020-03585-z
10. Kind AJH, Buckingham WR. Making neighborhood-disadvantage metrics accessible—The Neighborhood Atlas. *N Engl J Med*. 2018;378:2456-2458. doi:10.1056/NEJMp1802313
11. American Medical Association (AMA). New AMA policies recognize race as a social, not biological, construct [press release]. AMA; November 16, 2020. Accessed April 10, 2021. https://www.ama-assn.org/press-center/press-releases/new-ama-policies-recognize-race-social-not-biological-construct
12. American Cancer Society Cancer Action Network. Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer: A Landscape Report. Accessed March 4, 2019. https://www.fightcancer.org/sites/default/files/National%20Documents/Clinical-Trials-Landscape-Report.pdf