Cancer Clinical Trial Enrollment: OK Doc, but What's in It for Me?

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"Mr. S no longer wants to participate in the trial." I pause in the middle of the hallway, looking at my resident in surprise. The patient I was on my way to examine had seemed so enthusiastic about it at the initial consult. Mr. S is a polite and physically robust white man without serious medical comorbidities who prioritizes continuing his full-time job during his treatment. I enter the examination room and, just as I did a few days prior, sit down to describe why he is eligible for a promising national cooperative group phase III trial studying the efficacy and tolerability of adding immunotherapy to standard-of-care chemoradiotherapy, and express how excited I am that this trial had opened just in time for him. He smiles but shakes his head. "OK, Doc, but what's in it for me? As much as I want to help other people, it seems like all the potential side effects and extra visits might be too much for me right now."

As oncologists, we strive to provide our patients with the highest quality care possible and to advance the field as potential new treatments become available. Clinical trials are an essential part of both aspects of this mission. On the portion of their website geared toward patients, NCCN has noted that "patients enrolled in clinical trials receive the best management of care."[1] However, studies have shown that <5% of patients with cancer enroll in clinical trials at all,[2] even though a recent survey showed that a vast majority would strongly consider doing so.[3]

At the same time, studies suggest multilevel barriers to clinical trial accrual, especially for patients who are elderly, adolescent or young adult, female, ethnic/racial minorities, or socioeconomically disadvantaged.[4] Patients may be burdened by the expenses of travel to and lodging near a trial site, taking time from work, and arranging care for dependent family members.[5] Physicians may be frustrated by the complexities of trial design and execution, including the lack of infrastructure, funding support, and/or incentives to actively promote accrual amid their busy clinical activities. Other factors may include patient mistrust of investigators, language and other communication barriers, delays in starting treatment, and overly stringent eligibility criteria and tissue/imaging requirements.

With this context in mind, in a study published in this issue of *JNCCN*, Zaorsky et al[6] used the National Cancer Database (NCDB) not only to examine the prevalence of clinical trial enrollment specifically at the initial cancer diagnosis but also to determine whether trial accrual would be associated with overall survival. The authors report a 0.1% rate of clinical trial enrollment among treatment-naïve patients with cancer in the United States. This estimation is limited by the fact that the NCDB is hospital-based rather than population-based, only including Commission on Cancer–accredited facilities and is therefore not necessarily representative of the US population overall.[7] Additionally, a variable like clinical trial accrual may be underascertained in an administrative database. However, the results from this study are concordant with findings in the existing literature, showing that clinical trial accrual remains unacceptably low and that significant disparities according to race, insurance status, and comorbidities are persistent.[2]

More novel is Zaorsky et al's finding that patients who enrolled in clinical trials had significantly improved overall survival compared with those who did not.[6]

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Although this large national observational study may have inherent selection biases, these data are certainly compelling. Could it be that simply enrolling in a clinical trial (regardless of disease site, phase, intervention, or randomization arm) leads to an improvement in outcomes due to improved supportive care, care coordination, surveillance, and quality assurance?[8] Or is it that patients who are able to surpass all the barriers to clinical trial enrollment are inherently at a lower risk of death compared with an unselected cohort treated off-trial (some of whom may have been deemed ineligible for trial enrollment due to poor functional status or life expectancy, or who were treated at low-volume facilities without comprehensive multidisciplinary expertise)?

Fortunately, there is a high level of interest in determining practical solutions to low trial accrual. ASCO assembled a Cancer Trial Accrual Symposium in 2013, with recommendations in favor of promoting equity in accrual by providing financial support, engaging with patients and providers in minority and/or under-resourced communities, and incentivizing physician involvement.[9] Community-based pilot programs implementing these recommendations have begun operating successfully,[10] and digital media platforms like TheMedNet hold promise in connecting patients and providers to active trials with which they may not otherwise have been familiar.

Ultimately, to make a major dent in improving clinical trial enrollment overall, we must also consider the question that many patients might be asking themselves: "What's in it for me?" For all the altruism that patients may possess, a new diagnosis of cancer and the anticipation of toxic treatments can be overwhelming. They will and should choose to do what they believe is best for themselves and their families, not necessarily society at large. The evidence provided by Zaorsky et al[6] in this issue should propel further research characterizing the value of clinical trial enrollment for the individual participants. Perhaps if we had enough data to convince Mr. S that remaining on trial would improve his *own* prognosis, we might be able to tip the scales in his complex decision-making process.

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