Discussion of 2021-1730

DISPARITY IN CLINICAL TRIAL PARTICIPATION AMONG PATIENTS WITH GASTROINTESTINAL CANCER

**DR SYED A AHMAD** (Cincinnati, OH): At this year's European Society for Medical Oncology Congress 2021, Dr Joseph Unger from Fred Hutchinson Cancer Center and Dr Charles Blanke, the Director of Southwest Oncology Group, presented a fascinating and remarkable abstract highlighting the importance of clinical trials. The authors evaluated phase II trials from adult National Clinical Trials Network (NCTN) groups that included the Southwest Oncology Group (SWOG), Alliance, NRG Oncology, and the Eastern Cooperative Oncology Group, reported from 1980 onward, with statistically significant findings. In total, 163 trials, including 108,000 patients were evaluated. These trials were estimated to have generated gains of 14 million life-years to cancer patients. This analysis highlights the importance of clinical trials, the role of drug discovery, and the critical role of government-sponsored cancer research in extending the lives of patients with cancer. However, if the results in these studies are to be applicable to broad populations, the trial participants must reflect as much as possible the population of patients with the disease. We know that differences in response to therapy can exist among different ethnic and racial populations based on nuclear polymorphisms, pharmacogenomics, and other factors.

I want to congratulate the authors on a very important study highlighting the fact that we have not done a great job enrolling a diverse population on to our NCTN clinical studies. Consistent with your results, a recent paper published in *JAMA Oncology* by Loury demonstrated that clinical trials completed over the last decade had only 22% of expected proportions of black patients and 44% of expected proportions of Hispanic patients. Your study is unique in that it highlights clinical trial participation with surgical gastrointestinal trials only. The major finding from your study that resonated with me was that trial participation in general has decreased over time. Consistent with past studies, Black patients, Asian patients, Medicare patients, and the less educated were least likely to enroll in trials, and within diverse populations, income and education did not necessarily reverse the trend.

Your comparison group was the National Cancer Database (NCDB). The NCDB is really a hospital‑based dataset and not a population‑based dataset. It is also subject to inherent selection bias that may confound analysis of diverse populations. As such, it may not represent the diverse population that needs to be enrolled on to clinical trials. Furthermore, most patients within the database may not have been qualified for inclusion into most of the studies, or the studies may not have been available to the patients within the database. Is the NCDB a true representation of our diverse population?

Part of your analysis evaluated clinical trial slots for year of enrollment. However, many of the 36 National Cancer Institute (NCI) studies you evaluated were not completed and closed prematurely. Thus, those trial slots were not available. As an example, the SWOG 0425 study on gastric cancer closed prematurely after enrolling only 7 patients. Did you account for these early closures in trial availability when completing your analysis?

Did you evaluate where these 36 studies were open? Were they intergroup studies, open at only academic hospitals? How many were open through the NCI Community Oncology Research Program (NCORP) mechanisms and available at community hospitals?

More recently, to quickly accrue and complete studies, a phenomenon of globalization of trials has taken a foothold. Thus, many NCTN trials were opened in Europe, where diversity is even more of an issue. Please comment on this.

How do we fix these issues? There are many barriers to clinical trial enrollment for diverse populations, such as patient attitudes regarding clinical trials, lack of trust in the healthcare system (and in doctors), physician attitudes that certain populations will not be able to understand the study or manage the responsibility of being on the study, structural issues for diverse populations, lack of insurance to cover the cost of participation, inability to pay the copays that are required for visits, not having the extra time required to be in the study, transportation barriers, child care barriers, time off from work barriers, and a lack of physical access to the studies.

**DR SELWYN M VICKERS** (Birmingham, AL): I want to commend Dr Pawlik for establishing a platform to continually evaluate issues related to disparity in cancer care in clinical trials. This is important because, as he has outlined, clinical trials are arguably the standard of care and should be the standard of care in NCI comprehensive cancer centers. The types of cancer he outlined also happen to have survival of less than 50%, which is the reason this should be a part of the standard of care vs what we see as optional and elective. For the last 3-4 years, I led 2 large U wards, a U‑24 and a U‑54, that looked solely at increasing the rate of minority enrollment in clinical trials. It involved 5 comprehensive cancer centers at the University of Alabama at Birmingham, Minnesota, MD Anderson, Johns Hopkins, and the University of California, Davis. This program sought to answer some of the things that Dr Pawlik put on the table.

In large part, without going into full detail, the challenges are based on provider bias, provider ignorance, patient education, and trust. We were able to increase minority enrollment in clinical trials by 2 to 3‑fold, largely through clinical trial navigators, who created a paradigm of trust for people entering a space that was foreign to them. We were also able to help encourage a change in the thought process of providers who, as I think Dr Ahmad mentioned, may think, “Why am I going to waste my time on a person who will not make their appointment, who will not understand the trial, and who does not look like me?” This line of thinking in American medicine has been a challenge for us all.

The incidents in Tuskegee were magnified during COVID‑19. Our lack of tolerance for disparity was turned into a flaming fire as we saw the number of deaths rise in patients who suffered from those social determinants of health.

This study was neatly done by taking the clinical trials evaluation program and looking at those diseases for which people were enrolled and comparing them with a large database. There are clearly limitations to what you can determine from that, but I think you brought to bear the things we have worried about and believe exist. Our study showed that the actual enrollment for clinical trials for all‑comers in cancer is about 3%, and for minorities, it is 0.3%. So, moving the bar is significantly important, and yet it is an easy thing, to some degree, to improve on those numbers if we make the effort.

I have a few questions. When you looked at the discriminating factors related to income and the social determinants of health given to you by zip code, what are the other surrogates that you can find from this study that helped determine the issues of trust? Some factors that should lead people to be more interested in enrollment did not, so you obviously came away believing there is a lack of trust as a critical part of these patients’ ability to engage in trials.

You identified an unusual paradigm that higher income people of color and higher income White patients both had a lower propensity to enroll in certain trials than lower income people of color and lower income White patients. What does this data mean? It seems that that group would be more likely to enroll in trials or have an interest in trials moving forward.

Is there any data on cost? One of the concerns of patients seeking to enroll in a trial is whether their insurance will cover it, and also, providers' understanding of the cost they will either incur themselves or put on the patient. This data may be discovered in the financial arm of the databases.

**DR RYAN FIELDS** (St Louis, MO): Some interesting work has been done recently by the American Cancer Society. Their Action Network, which is their patient advocacy group led by Mark Fleury, who is a PhD scientist, came up with some interesting observations on clinical trial participation. The 2 I think are relevant here are that for patients across the board, the number 1 reason for not participating in a trial was not having been offered a trial, which points to that 3% enrollment. Patients are often simply not presented with a trial. And when they were, the number 1 reason for not participating, again across the spectrum, was things related to travel and out‑of‑pocket cost. How do we surmount those problems? How do we at the cancer-center level address that?

Are there mechanisms in place to look at that as a barrier and try to overcome it? And, of course, increase trial awareness? I think that may point to why, regardless of income level, income in minority patients is not necessary a surrogate if they are not being offered a trial for reasons of unconscious bias and others.

**DR ALEX PARIKH** (Greenville, NC): One of the other factors that seemed very important in terms of association with lack of trial involvement was the insurance aspect, particularly Medicare, where the hazard ratio, I believe, was 0.46 (as well as age). As our growing population increases in age, more patients will have Medicare, so, how do you think we can combat that?

Were there any racial associations for patients with Medicare? In other words, in patients with Medicare, are African American patients less likely to enroll in clinical trials?

**DR JOHN CAMERON** (Baltimore, MD): There are a couple of problems with getting people to enroll in clinical trials that I wonder how you confront. One is that a lot of people are afraid of entering a trial because they do not want to be experimented on.

Second, they want to know which arm is the best arm, because they want to be put in that arm, or they do not want to participate in the study. So, how do you overcome those 2 factors?

**DR ADRIAN DIAZ** (Columbus, OH): To begin with Dr Ahmad's questions, the NCDB absolutely has its limitations. We could have alternatively used population rates for cancer, however, we wanted to ascribe some other metrics, such as income, education, all those social determinants of health, and that is not available on the population level. The NCDB does, at a patient level, provide that information. Furthermore, similar studies in non‑gastrointestinal cancer have used the NCDB in a similar way and have validated the approach. For those reasons, we thought that using the NCDB was a stronger approach.

In terms of years of the years of enrollment reported, we used the years reported to us by clinicaltrials.gov and the Clinical Trials Monitoring Branch. So, if a trial did close early, or there were fewer enrollees or fewer spots available for 1 year that was reported to us, that is the number of open slots that we used for our analysis.

In terms of whether we addressed where these trials were opened, we do not. Frankly, it is an excellent question. I think future work and the next steps are assessing where these trials are being offered. Clearly, there is a rural‑urban disparity, in not just clinical trials but all of healthcare, and I think that needs to be assessed.

Furthermore, I think there is an opportunity to perform not just a macro study like this but a micro-investigation into which institutions are the positive deviants that are enrolling a diverse group of patients into their clinical trials, and how the rest of us can learn from them. So, I think that is an excellent opportunity.

In terms of globalization of clinical trials, whether it is a good idea or a bad idea, I think it is irrelevant. I think the horse is out of the barn, and we have seen in some of the COVID trials over last 2 years, how global they have been and how quickly we have been able to come to an answer. I think the real question is, is how do we make global trials efficient, equitable, and fair for everyone, so that we can quickly determine the efficiency and the efficacy of our clinical question?

In terms of Dr Vickers' question about trust, there is really nothing in the database that we can use to determine trust. There are some surrogates, as you alluded to, such as education and income. But I will remind you, these were at the zip-code level, so we do not have patient-level data to determine that. I think what this data highlights is that there is a role for a qualitative assessment in interviewing patients, as others have done, to identify some of the barriers to trial enrollment; trust in particular.

In terms of income and intersectionality between income and race, I think we have seen this bear out in a couple studies from our group and others. To highlight a quick anecdote, I had a mentor tell me that she, as an African American Attending, living in a high-income neighborhood, was still at higher risk of maternal morbidity and maternal mortality than her White counterparts, and it was this phenomenon of income not really correcting for longstanding structural barriers that she has dealt with during her life. I think about it as equity in health, not just equity that we acquire in our homes and wealth, but equity in health, as well.

So, I think some recent studies are showing is that there is widening disparity between Black and White patients as you move up the income ladder. So, why that is happening? I think a lot of it has to do with trust. I also think a lot of it has to do with structural barriers in that at the higher income strata, Black patients just do not have access to the same resources that high-income White patients do.

In terms of the question of cost, in our database, we were unable to ascertain the direct cost to patients. I think that cost, in not just clinical trials but all of healthcare, is front and center for all our patients. We have recently seen surprise billing, and even in the era of the Affordable Care Act, many patients will be bankrupt from healthcare. It is a real concern, and there needs to be a lot more education about the upfront cost of clinical trials, but, as many of you have alluded, there is also the hidden cost of clinical trials, and that is taking time off from work or the cost of travel to an institution that might not be in your local community, and the cost of your family potentially having to be the primary caretaker. So, I think it is a question ripe for some different methods, qualitative methods to assess some of these challenges.

Regarding the interaction between insurance and age, I think that what we are seeing here is probably a phenomenon of collinearity. Medicare patients are, for the most part, older than 65, and patients who are older than 65 tend to have higher rates of frailty and disability. I think that highlights some of the structural barriers in clinical trials, in the way their inclusion and exclusion criteria may be written, which creates disparity for patients who might have a higher rate of frailty, or comorbidity, or disability. That, too, is a disparity. It is age and not just disparity of racism or income. It is an interesting phenomenon that we and others have seen, and it bears further investigation.

Regarding the interaction between Medicare and African American or Black patients, there was not a statistically significant interaction there, but I will mention that Medicare and, in particular, the Medicare datasets, are particularly underrepresentative of African Americans. The proportion of African Americans over 65 years of age is somewhere around 15% and, for reasons that are unknown to me and other investigators, Medicare has only about 8% of African Americans. It is certainly an issue as we ask these questions of the data.

I think the elephant in the room is, how do we fix this? I would say that this is not a problem in just clinical trials. This is a problem in all of healthcare. I think by addressing these globally, we will begin to also address them in clinical trials. So, those are things that Dr Higgins alluded to: diversifying the pipeline, diversifying our providers, and things that Dr Vickers alluded to. As lay clinical navigators, we should certainly begin to address issues of trust and issues of navigating the health system.

So, there is certainly not a single answer or response to how we fix this problem, but I think there are possible interventions at every level, from the local level all the way down to our own institutions, and I know that we at Ohio State are looking at our own data and ways to improve enrollment in our own trials.

Finally, how do we address this in clinical trials, specifically? I do not have the answer to this, but I think we can certainly tie enrollment, and diversity in enrollment, to things that we, as providers, care about, and that is NCI designation and accolades as such. And we can also tie it to future clinical trials and getting funding for future clinical trials, and tie that to our past performance, so that we not only learn from ourselves but learn from the positive deviants who are doing a really good job of diversifying their own clinical trials.