PRECISION ONCOLOGY NEWS

MSK Study Finds Survival Gap Between Clinical Trial, Real-World Patients on Approved Cancer Drugs

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NEW YORK – Medicare-covered patients with metastatic cancers are not experiencing the same survival outcomes on US Food and Drug Administration-approved treatments as patients involved in those treatments' pivotal clinical trials, according to a Memorial Sloan Kettering Cancer Center analysis published last week in *JAMA Network*.

The discrepancy underscores the need to include patients in clinical trials who adequately represent the population of patients that the treatments are intended to benefit — including those patients who are older than 65, the population covered under Medicare. The findings hold particular weight in light of the increasing trend toward targeted cancer treatments entering the market for biomarker-defined patient populations, since many of the clinical trials supporting approval for these drugs enroll sample sizes too small to stratify by factors beyond biomarker status. Trials like these, in many cases, are not powered to measure survival outcomes according to characteristics such as ethnicity or age.

"One of the concerns we had [going into the study] was that clinical trials are largely done in idealized settings," Sham Mailankody of MSK, one of the lead authors of the *JAMA Network* study, said. "So, patients generally tend to be younger, healthier, less diverse, and have fewer comorbidities and better performance status … and that's not always the patients we see in clinical practice."

Specifically, Mailankody and colleagues found a median survival difference of 6.3 months between the Medicare patients and the clinical trial participants treated across 29 indications for 22 treatments approved from 2008 to 2013. In all but one case, patients who received the drugs in clinical trials lived longer than patients in the real-world, Medicare-covered population. In instances where data were available, the real-world patients also required more dose reductions than the trial populations and were treated for shorter durations.

To conduct the analysis, the researchers used data from the Surveillance, Epidemiology, and End Results (SEER) database, which is linked with Medicare data capturing patients' treatment and date and cause of death. They compared data from patients who had specifically received a treatment for which the pivotal trial — that is, the trial that resulted in FDA approval — included overall survival results for the intervention arm. Because data included in the SEER-Medicare database do not extend beyond survival to include outcomes such as tumor shrinkage or progression-free survival times, the researchers could not include drugs approved based on surrogate endpoints in their analysis. This limitation is worth noting because the FDA is increasingly approving drugs on the basis of metrics such as response rates or progression-free survival, and in many cases, these pivotal trials powered to assess surrogate endpoints enroll smaller sample sizes of patients.

"The size of clinical trials for drug approvals is getting smaller over time … which does raise some of these questions of subgroups and representativeness," Mailankody said.

All in all, in more than 40 percent of the indications the researchers considered, the median survival observed in the SEER-Medicare patients, which consisted of 9,178 patients total, was less than half of the

median survival seen among the clinical trial-treated patients.

Though the analysis included drugs that were and were not approved for biomarker-defined populations of patients, a closer look at how the targeted agents measured up in the real world versus their clinical trials paints a stark picture. In the pivotal clinical trial for dabrafenib (Novartis' Taflinar), which was approved in 2013, for instance, the median overall survival seen among melanoma patients with BRAF V600E mutations treated with the agent was nearly 20 months. In the real-world Medicare population, this outcome was cut in half; the median overall survival in the real-world Medicare cohort was just 9.8 months.

While biomarker testing data are not included in the SEER-Medicare database, Mailankody and colleagues conducted their analysis with the presumed presence of biomarkers when relevant; the patients' disease types and stage matched the FDA indication for each given drug, but the researchers were limited in how much more specific they could get about these patients' cancers.

Another important limitation that Mailankody was careful to highlight was the fact that, unlike the clinical trials, the SEER-Medicare survival data lacked a control arm. Accordingly, the researchers could not look at the shorter survival durations seen in the real world relative to the survival durations seen for patients who did not receive the drug in the real world. The relative survival benefit — that is, how much longer Medicare patients lived with the FDA-approved treatments versus without them — compared to the survival benefits seen across the clinical trials would paint a fuller picture of these discrepancies, but those data were unavailable.

Age and comorbidities

Mailankody and colleagues did, however, have the necessary data to assess the presence of comorbidities in the Medicare population, which they used to limit their analysis only to patients with one or no comorbidities. This was an important step, Mailankody explained, in part because clinical trials often limit patient enrollment to ensure that comorbidities do not confound results. But even when patients with more than one comorbidity were excluded, the survival disparities remained.

"As a clinical investigator myself who runs studies, I know there are lots of reasons why trials need to be conducted in idealized settings … so there are definitely legitimate reasons for why trials cannot be as representative as the patients we see in the clinic," Mailankody acknowledged. "That said, even for rare cancers, with committed efforts, multicenter efforts, and multinational efforts, it is possible to enroll an adequate number of patients to answer some of these questions."

With enough patients enrolled across diverse age groups and backgrounds, clinical trials could, in theory, report survival outcomes according to key characteristics, including age. Only six of the clinical trials included in the MSK analysis reported these age-stratified survival outcomes.

Interestingly, the survivals reported for patients older than 65 in these six trials were comparable to the median overall survivals for all patients treated on the trials, but still significantly shorter than the 65-or-older patients treated in the real-world setting. While the fact that there were only six trials that reported these data made the finding more anecdotal than telling, Mailankody pointed this out to highlight that the discrepancies in survival between the clinical trial groups and the real-world Medicare group are likely multifaceted.

"I don't think that there's one factor like age or comorbidities or something else … it's probably a combination of these factors that explain the findings," Mailankody said.

Progress and implications

Rather than viewing the study findings as reason not to prescribe these FDA-approved treatments to elderly patients in the real world, Mailankody suggested that the findings should be interpreted more as a call to action to enroll more representative patient populations in clinical trials. Doing so would help provide oncologists and patients with fuller, more realistic understandings of how well FDA-approved drugs might work in their specific cases.

"This is an important piece of information for shared decision-making … for patients and doctors to realize that, particularly in patients who have comorbidities or other factors that are not covered in the trials, the outcomes may be more modest," he said. "And we should make continued efforts to enroll more representative trials so that we're able to more accurately identify the benefits of these therapies in the relevant subgroups of patients that have these cancers."

Considering that the MSK analysis included drugs approved only until 2013, the question remains as to whether these clinical trial-versus-real-world survival discrepancies have narrowed in the eight years since. While Mailankody acknowledged that the conversation has certainly garnered more attention across a variety of stakeholders as of late, the actual numbers haven't necessarily reflected this. The FDA did publish guidance last year encouraging the field to expand eligibility criteria for clinical trials, but any improvement in this regard has yet to play out.

"Other groups have looked at representativeness of clinical trials over time … and it doesn't look like we've done a whole lot of progress along those lines over the last 10 to 15 years," Mailankody said.

Indeed, data from the FDA's Drug Trials Snapshots website — an effort on the agency's part to bring transparency to the issue of clinical trial representation — show that precision oncology drugs within the last few years have consistently underenrolled minority patient populations, and in many cases, the same is true of elderly patient populations.

In the trial that led to the most recent precision oncology drug approval for which data are available on the Drug Trials Snapshot site, for instance — a December approval for margetuximab-cmkb (MacroGenics' Margenza) for HER2-positive breast cancer patients — 79 percent of patients in the trial were younger than 65 years of age, and only 4 percent were older than 75. In contrast, over 20 percent of patients diagnosed with breast cancer in the real world are over 75.

As increasingly narrow biomarker-defined FDA approvals continue to pick up steam, so too will the challenges of enrolling enough patients with certain molecular characteristics to conduct trials for these drugs. As such, Mailankody acknowledged that in some cases the urgency of getting a drug to the market might stand at odds with the amount of time and resources required to enroll fully representative cohorts of patients. But with these narrowly defined precision oncology drugs in particular, he said, drug developers could at least partially overcome this challenge by conducting post-market trials and analyses.

"For those rare tumor types or subgroups, it is possible for regulatory agencies or investigators to follow up after the approval of the drug ... to try to characterize and collect data that more accurately reflects the real-world population," he said. "I don't think we should be waiting for these perfectly done studies to get drugs to the market, but when the data are limited, there is some responsibility on all of us to then collect data after the drug has been approved in those relevant subgroups and ensure that the results seen in the pivotal study are mirrored in the real-world use of these drugs."

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