Cancer Trials: Is Progression-Free Survival Enough?

By James Miessler

A new study questions the use of progression-free survival as a surrogate endpoint in cancer clinical trials after finding it overlooks quality of life issues.

Progression-free survival (PFS) has become a frequent outcome used to evaluate new cancer drug efficacy.

But Canadian researchers failed to find a substantial link between PFS and health-related quality of life (HRQoL) in cancer trials, casting doubt on its role as a surrogate endpoint.

Lead investigators Sean Alexander Kennedy, Bruno Kovic and Xuejing Jin analyzed the results of 38 randomized oncology trials to try to pin down the connection between patients’ length of survival and quality of life.

They evaluated trials that focused on intravenous, oral, intraportal or intrapleural chemotherapy or biological treatments and reported progression-free survival or health-related quality of life.

Their findings, published in JAMA Internal Medicine, suggest PFS benefits are unrelated to improved quality-of-life scores reported by patients — and don’t always translate into an overall survival (OS) benefit, an objective endpoint representing the duration of survival that’s viewed as the most important cancer trial outcome.

The report says there are only two possible reasons to use progression-free survival.

Timing is Key in Parkinson’s Clinical Trials

By Bill Myers

A Florida scientist is urging sponsors and care providers to do a better job of getting early-stage Parkinson’s sufferers into clinical trials before they start treatment.

Robert A. Hauser, director of the Parkinson’s & Movement Disorder Center at the University of South Florida and author of one of the most widely used patient diaries for Parkinson’s trials, says researchers need to recruit patients at the first sign of trouble — before they start taking meds so they have time to assess experimental therapies against placebos.

The critical time to enroll patients is during their so-called Golden Year — that is, as soon as they’re diagnosed with “mild classic motor features until they truly require symptomatic therapy,” Hauser said.

This gives both researchers and patients the best shot at coming up with a treatment that may stave off symptoms and prevent disease progression, he tells CenterWatch.

Hauser says his clinic is part of at least four early-stage Parkinson’s trials, two privately sponsored and two funded by a combination of grants from private foundations and the National Institutes of Health. There are about 20 participants in total in those studies but Hauser says he’s lost count of the number of patients who came to see him long after their symptoms started and it was too late to enroll them.

“My experience is a lot of patients come
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FDA Guidance: Start with Kids in Atopic Dermatitis Trials
Sponsors of atopic dermatitis drugs for children don’t have to wait to test a drug’s safety or efficacy on adults before beginning pediatric trials, the FDA says.

The new guidance, released last week, reverses longstanding FDA recommendations that drugs trying to treat a disease by affecting the entire body start with adult trials.

Atopic dermatitis is the dry, itchy rash caused by eczema that affects nearly 18 million Americans, most of them children. It often clusters with asthma and hay fever.

The agency says its U-turn was prompted by recommendations from a 2015 meeting of its Dermatologic and Ophthalmic Drug Advisory Committee.

The FDA acknowledges that “some major safety questions” may be left open before trials can begin.

But it says it’s “not generally necessary to have an extensive safety database in adults before initiating pediatric studies” as long as the disease isn’t potentially fatal to pediatric populations and there’s a risk doctors may be prescribing therapies off-label before trials wrap up.

Trials will have to consider a drug’s effect on children of all ages, including toddlers and infants, the guidance adds.

Sponsors may have to start with older children first if specific data from an older subpopulation can help inform the study, if there’s an “age-related technical issue” or if there is some reason to worry about a drug’s safety in younger children.


Re-Trials for Pediatrics Pay Off
The FDA’s pediatric exclusivity rules allowed drugmakers to reap a 680 percent return on their investments, a new analysis finds.

The Best Pharmaceuticals for Children Act of 2002 offered drugmakers six months of market exclusivity in return for running drugs already approved for adults through clinical trials again to test their safety and efficacy for children.

Congress passed the measure because it was concerned that doctors were prescribing adult meds to kids off-label and the pharmaceutical industry argued that limited exclusivity provided proper incentive to invest in fresh trials.

The incentive has proved lucrative, according to the analysis published in JAMA Internal Medicine.

Study author Michael S. Sinha and his colleagues at Boston’s Brigham and Women’s Hospital examined 54 drugs given exclusivity between 2007 and 2012.

They estimate pharma companies spent an average of $36.4 million to re-test their drugs in clinical trials and the median net return was $176 million—a ratio of about 680 percent.

“Meaningful knowledge of pediatric uses of pharmaceuticals has come from the pediatric exclusivity program, but at a high cost” in hefty drug prices passed along to consumers, Sinha said, noting that “other approaches … such as direct funding” for pediatric trials “may be more economically efficient.”

Advanced Cancer Trials Set
The FDA has greenlighted clinical trials for a Chinese biotech hoping to treat non-Hodgkin’s lymphoma, ovarian cancer and other advanced cancers.

Innovent Biologics is planning several trials on IBI-188, an anti-CD47 monoclonal antibody, which works by boosting patients’ immune systems and setting up markers on cancer cells for targeted treatments that spare surrounding healthy tissue.

There are about 14 ongoing clinical trials on these types of meds. But Innovent is the first Chinese company given the nod to test such a treatment.

In January, the FDA gave Innovent the go-ahead for clinical trials of Sintilimab, an anti-PD-1 antibody that also targets cancer.

Personalized Pain Trial Scores Big on Patient Satisfaction Scale
Patients gave thumbs up to a clinical trial that provided a menu of a la carte treatment options even though it didn’t make a dramatic difference in managing their pain.

In what’s believe to be the largest trial of its kind, a team at the University of California, Davis, enrolled 215 people in a single-patient multi-crossover trial to test pain management.

Often called n-of-1 trials, the single-patient, multi-crossover approach allows participants to switch between two or more therapies during the trial and allows researchers to gauge the effect of treatments on each individual.

Researchers randomly assigned 108 of the pain patients to personalized mini-trials in which they were given eight different treatment options, ranging from opioids to acupuncture, to try for between four to 12 weeks.

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Industry Briefs

Participants were also given access to an open-source mobile app called Trialist, which sent reminders about beginning each treatment, daily questionnaires rating their pain, and warnings about possible side effects of their selected treatments.

The remaining 107 volunteers continued using their same pre-trial treatment. Researchers measured patients’ pain management as well as their level of satisfaction with their treatment.

Patients in the n-of-1 trials group reported slight but statistically insignificant improvement in pain symptoms but still raved about their experience. For instance, 88 percent said Trialist was “extremely or very helpful” in keeping track of their pain.

The team reported its findings in *JAMA Internal Medicine*, which carried a separate editorial praising the trial for its “ambition.”

**ACRES: Accreditation of Trial Sites**

A nonprofit group has begun evaluating standards for first-of-its kind voluntary accreditation of clinical research sites as part of a new effort to enhance quality and speed development of new medical products worldwide.

The Alliance for Clinical Research Excellence and Safety (ACRES) is currently performing its first evaluation at research facilities owned by ActivMed, a company in Massachusetts that’s completed 720 clinical trials since it was founded in 1994.

ACRES officials believe accrediting site performance and research quality can “dramatically” shrink both the costs and time spent on clinical trials.

As part of its effort, the company is working on technology dubbed “Dynamic Accreditation” to provide real-time feedback to sites, sponsors, CROs, regulators and patients about site performance.

“The idea of site accreditation is an important one. We are sure that both our site and ACRES will learn more as we move through the beta-testing of the standards,” said Terry Stubbs, ActivMed president and CEO.

Once the pilot program wraps up, ACRES will commission an independent study to assess its impact.

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**Medical Device Guidance**

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as an endpoint in oncology — the belief that it’s a valid surrogate marker for overall survival and the assumption that patients who live longer without disease progression — even without longer survival — will experience a higher quality of life.

But according to current evidence, progression-free survival is too unpredictable and inconsistent to serve as a viable surrogate for overall survival.

“[PFS] association with improved [health-related quality of life] is far from self-evident,” the study says, “because HRQoL is likely to be impaired by adverse events resulting from the treatments responsible for prolonged” progression-free survival.

According to current evidence, progression-free survival is too unpredictable and inconsistent to serve as a viable surrogate for overall survival.

—Study published in JAMA Internal Medicine

Oncological experts have questioned whether it’s appropriate to use PFS to evaluate treatments given the uncertainties, the investigators say.

They note that progression-free survival is a frequent surrogate because shorter and smaller trials can be used to measure it, making it more convenient.

It’s also a popular measure in FDA drug approvals. At least a dozen drugs approved by the agency over a five-year period used PFS as a primary endpoint.

Its use as a surrogate outcome has also been popular in clinical trials due to limitations associated with overall survival that include higher costs, larger sample sizes, longer follow-up and confounding effects that come from crossover designs and post-progression therapies.

Researchers say their findings indicate clinical trials must be “adequately powered” for overall survival and/or designed for strict and accurate quality of life measurements to meet the needs of cancer patients.
Parkinson's Clinical Trials
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to us and say, 'I’m really here because my symptoms are bothering me.' Boy, if only this patient had come a year ago,” Hauser says.

He notes that patients, care providers and especially sponsors can play a critical role in early trial recruiting.

Parkinson's develops subtly — a tremor here, slight difficulty moving there, says Sofija Jovic, business transformation advisor at MedAvante-Prophase. Typically, patients have about six months to a year after displaying very early signs before requiring systemic therapies to address underlying symptoms.

Parkinson’s disease, and most other neuro-degenerative disorders, can hide for a long time because human brains are adaptable. That’s good news for stroke patients because the brain will dig new neural pathways. But it’s bad news for Parkinson’s sufferers because it generally means that by the time symptoms present their brain has literally run out of room to adapt.

“You have sort of a window during which there are enough symptoms for us to be sure that the person has this disease but it’s not so far gone that we’re not likely to see any improvement,” Jovic says.

As it stands, less than 3 percent of Parkinson’s patients enroll in clinical trials, Jovic says. Patients are a lot like the frog in the boiling water — they don’t realize there’s trouble until it’s already too late, she adds.

Recent discoveries that Parkinson’s appears to be related to the buildup of misfolded alpha-synuclein proteins — and that those protein clusters may respond to treatments — has given researchers renewed hope that they’re on a path toward effective treatments and even cures, Hauser says.

But he stresses that won’t happen without enough patients to recruit for clinical trials at the earliest, pre-med stages of the disease.

He admits that the subtlety of early-stage Parkinson’s creates “a Catch-22” of sorts. “How do we get this message to patients who don’t know there’s this message to be received?” he says.

The answer, he tells CenterWatch: Sponsors have to do a better job of getting the word out to doctors that they shouldn’t rush to prescribe systemic meds prematurely — and should instead refer patients to early clinical trials.

Jovic agrees that sponsors have to do a better job establishing relationships with care providers. But she says they also need to develop technology that enables virtual trials because neuro-degenerative disorders don’t lend themselves to site visits.

“You have a patient who’s been up half the night, and you’re going to ask his caregiver to drive him two hours to a site for four hours of tests?” Jovic says. “That’s just not realistic.”

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