Progression-free survival, patient-reported outcomes, and the Holy Grail

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In oncology clinical trials, overall survival (OS) remains the gold standard for clinical benefit. However, because there are so many available treatment options for most types of cancer, survival analysis in clinical trials is often confounded by subsequent therapies. Progression-free survival (PFS) is an endpoint not so confounded, and one that requires fewer patients and less time to arrive at a conclusion about a new therapy. As a result, an ever-increasing number of oncology clinical trials are launched in which PFS is used as the primary endpoint. Several years ago, Pazdur[1] emphasized that the time-to-progression endpoint must use the same evaluation techniques and schedules for all treatment arms and he recommended blinding of trials or at minimum, the use of an external blinded radiographic review committee. He also noted that improvement in disease-related symptoms qualifies as clinical benefit and may therefore be an appropriate endpoint for drug approval.

Since that time, PFS has been the basis for approval of many – perhaps even most – oncology drugs. In contrast, symptom benefit or other quality-of-life endpoints are rarely the basis for approval. During 2006-2010, there were 16 approved oncology drugs in which a patient-reported outcome (PRO) claim was submitted. None of those drugs received approval for a symptom or PRO label claim.[2] Why is this? There are many reasons, but perhaps the most fundamental one is that the US Food and Drug Administration (FDA) has a strong preference for data that demonstrate symptom improvement rather than delay in symptom worsening. From a regulatory perspective, there is a good reason for this. Consider a comparison of standard, toxic chemotherapy and a better-tolerated but less effective experimental therapy. Approval based on time to worsening of symptoms might actually make the standard, more effective therapy look worse (in the short run). This would clearly be a problem to a regulatory body, allowing inferior therapies to replace more effective therapies merely because they don't make people feel as badly.

However, there is an imperative in oncology drug development that provides us with an incentive to find a way to introduce symptom and PRO endpoints more formally into the regulatory scene. First, to maximize the potential benefit observed, virtually all oncology clinical trials restrict eligibility to patients with good performance status. By definition, these are patients with few or no disease-related symptoms. Therefore, there is not much that can be improved upon, so a symptom improvement goal is not realistic. Delay of onset of disease-related symptoms is, however, a meaningful endpoint to patients.

Second, and more important, disease symptom benefit and related patient-based outcomes, such as side effect burden and treatment tolerability, are critical to determining whether PFS as an endpoint has any value at all. In the absence of an OS benefit, PFS is a difficult endpoint to place a value upon. On the one hand, delaying cancer progression is likely to confer some benefit to a person's quality of life, not only because of the psychological benefit of knowing one's disease is stable, but also because delaying progression is likely to delay the onset of life-limiting symptoms. On the other hand, treatment itself carries toxicities that can be distressing and life-limiting. In addition, there are costs associated with treatment that are placing an increasing burden on the financial wellbeing of patients and their families. To fully appreciate the benefits and risks associated with delaying PFS, these studies require assessment of targeted quality-of-life domains, namely disease symptoms, treatment side effects, acceptability of therapy, and financial cost.

With respect to the PRO aspect of oncology clinical trials, the implicit (or perhaps it should be explicit) hypothesis is that the treatment arm associated with a PFS benefit also confers a symptom or other PRO benefit relative to the comparator. This is based on the underlying hypothesis that the disease symptom benefit of delaying progression will be greater than any differences in toxicities that might exist between treatments. To test this hypothesis properly, it is critically important that all living patients be assessed even after progression, for the full follow-up window specified in the treatment protocol. If, as has been the case in many previous trials, PRO assessment stops at the time of progression, this will introduce a bias in the group com-

JCSO 2014;12:265-266. ©2014 Frontline Medical Communications. DOI 10.12788/jcso.0061

parison, which typically disadvantages the more effective treatment because it retains more patients, including some who may have progressed on the inferior treatments.

What questions should be asked of patients to evaluate their perspective on treatment benefit? A primary emphasis on symptoms of disease makes sense, with the understanding that some symptoms, such as fatigue and nausea, may be due to both disease and treatment. A secondary emphasis on treatment side effects, and the burden or acceptability of treatment, should ideally also include a measure of patient preferences for continuing active treatment, whether with stable or responding disease parameters. After more than 30 years of studying PROs in oncology clinical trials, we are still working to come up with the best combination of questions to assess this rather complicated set of considerations. Perhaps it is a Holy Grail, but we are moving closer to the goal.

With respect to cost outcomes, although they are not in the mix when it comes to US regulatory review, they are increasingly important to our patients. Often, we find that noncytotoxic, targeted therapy provides significant clinical benefit above and beyond what is possible with conventional chemotherapy. They also tend to carry very high costs, more and more of which must come from the pockets of patients themselves. This adds new financial burdens to individuals and of course to us collectively, providing ever more incentive to ensure that new therapies that extend PFS are worth their cost. I don't think we can afford to live much longer by PFS alone. It's time we made sure that PFS is worth paying for, and the best source for determining that is our patients. We have all the tools to do this; now we must get better at putting them together.

With this editorial, I invite colleagues around the world to write to the journal with suggestions for how one might go about placing a value on PFS in the absence of a demonstrable OS benefit. For example, what weight should be given to disease symptom relief versus treatment toxicity? How important is it to know whether a symptom like nausea or fatigue is caused by the disease or by the treatment? How does one factor in cost beyond the current unsatisfying methods of cost effectiveness and cost-utility analysis? Please share your thoughts in 1,000 words or fewer and e-mail them to rmatthews@frontlinemedcom.com.

References

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