ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Is the Use of Progression-Free Survival a Valid Endpoint for Trials of Drug Combinations in Oncology?

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H&O What are the goals of treatment in cancer, and have they changed over the years?

IT The ultimate goals of treatment of any disease are twofold: to allow the patient to live longer and/or better. The use of overall survival as an endpoint can be complicated by the length of time patients are able to live with the disease. Therefore, study investigators tend to look at proximal endpoints that they hope can act as a surrogate for longer life or better quality of life. In oncology, response rates indicate the proportion of patients with a given degree of tumor shrinkage. Progression-free survival indicates how long the patient lives before the tumor starts to regrow or progress. This endpoint seems like it can provide valuable information. It could be argued that a patient will feel better if his or her tumors are not progressing. It is good news for the patient. However, cessation of disease progression must be balanced against the toxicity of the treatment. In addition, estimation of progression-free survival has hidden biases and has not been a good surrogate for overall survival or quality of life.

H&O What are the challenges in measuring the impact of oncology drug combinations in clinical trials?

IT It can be difficult to assess whether a new drug or combination is better than standard treatment. A randomized clinical trial should compare a new treatment, whether a novel drug or a new combination, vs the current standard treatment. The addition of a drug almost invariably confers added toxicity, with or without added benefit. A new curative treatment would be valuable even if it were associated with substantial toxicity. But if you have a treatment that adds only a month or 2 of life, then you need to balance the benefits against the downsides of toxicity and cost.

H&O What is the rationale for using progression-free survival as an endpoint in clinical trials in oncology?

IT Approximately 80% of registration trials now use progression-free survival as their primary endpoint. An improvement in progression-free survival can provide the basis for regulatory approval of a drug from the US Food and Drug Administration (FDA) and the European Medicines Agency. The rationale is that progression-free survival can be measured sooner than overall survival and therefore might allow an earlier assessment of benefit. In most cases, the disease progresses before a patient dies. A recent study showed that, on average, the use of progression-free survival expedites the drug approval process by approximately a year. Pharmaceutical companies retain the patent on a drug for a limited duration, so the sooner they can bring a drug to market, the better. The advantage of using progression-free survival is that it provides an answer regarding efficacy earlier than overall survival. The problem is whether the answer is correct.

H&O Are there any studies of whether improvement in progression-free survival corresponds to improvement in overall survival?

IT Many studies have evaluated this question. A few studies have shown a correlation between these outcomes, but,

in general, progression-free survival appears to be a poor surrogate for overall survival. Many studies have found a statistically significant difference in progression-free survival that did not translate into a significant difference in overall survival after longer-term assessment. In some cases, a bigger difference in progression-free survival led to a smaller difference in overall survival.

H&O What factors can contribute to differences in the rates of progression-free survival and overall survival?

IT Although a treatment may delay disease progression, once the tumor does begin to grow, it may do so more quickly. Any gain can be lost.

Analysis of drug combinations raises the question of whether a similar outcome could be achieved by using the drugs sequentially. Sequential use would likely be less expensive and less toxic.

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H&O Does progression-free survival provide insight into any type of improvement for drug combinations?

IT If a treatment does not improve progression-free survival, then it has no effect. If progression-free survival does improve, the effect might not be meaningful. Bias occurs when more patients in one arm of a study are withdrawn and censored before tumor progression is documented; this is known as informative censoring. In a previous analysis, my colleagues and I showed that the addition of an ineffective but toxic drug to standard treatment can cause patients to withdraw from a study, leading to an apparent improvement in progression-free survival as a result of this bias. Thus, improvement in progression-free survival can be an artifact and does not necessarily indicate therapeutic value of a drug.

H&O Is there an alternative endpoint?

IT I suggest replacing progression-free survival with time to treatment failure if an earlier endpoint than overall survival is needed. An endpoint of time to treatment failure would encompass disease progression, as well as drug discontinuation for tolerability issues or for any reason. Time to treatment failure is still not a perfect correlate with overall survival, but it would avoid the bias of informative censoring. The FDA rejected this endpoint as a basis for drug approval, which I think was a mistake.

H&O Do you have any other recommendations to improve the design of clinical trials in oncology?

IT Particularly in the setting of metastatic cancer, which has relatively short survival, overall survival and quality of life should be the primary endpoints. Progression-free survival should not be used in diseases associated with short-term survival. As an example, progression-free survival should not be used in studies of pancreatic cancer, where the median survival is approximately a year. When evaluating treatments in diseases with survival measured in multiple years, a more proximal endpoint is needed. Time to treatment failure or some other endpoint may be appropriate, depending on the disease. Early treatment of prostate cancer or breast cancer is very different from treatment of metastatic pancreatic, lung, or colon cancer.

There are several other problems confounding the results of clinical trials, including use of a nonstandard control group and underestimation of toxicity. These issues are beyond the scope of this discussion.

Disclosure

Dr Tannock has no relevant conflicts of interest to disclose.

Suggested Readings

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