Response Rates, Survival, and Chemotherapy Trials

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Early clinical trials of a novel oncology agent or combination regimen usually examine the biologic activity of the therapy using surrogate end points. These end points are believed to predict the clinical benefit of the new treatment, which is then tested in subsequent controlled, randomized clinical trials. The most commonly used surrogate end point, the response rate, has conventionally been examined in phase II trials and allows the early determination of the antitumor activity of the new therapy.

Response rate determinations reflect tumors that exhibit a complete regression or show a defined reduction for a specified time period. Stable tumors are excluded from response rate determinations. Accurate response rate determinations can be confounded by subjective biases introduced in unblinded clinical trials and inaccuracies of radiographic techniques and measurements.

Clinical benefit, a regulatory end point used in traditional drug approval, has generally been characterized by an increase in patient survival, an unambiguous gold standard of efficacy, or by relieving or delaying the onset of disease-related symptoms. The demonstration of improving survival may be obscured by subsequent therapies after disease progression in randomized trials. Relief of tumor-related symptoms has been difficult to document in oncology trials because of traditionally restrictive eligibility criteria that allow only asymptomatic or early symptomatic patients into the trials.

The link between surrogate end points and their ability to predict clinical benefit has produced controversy in the oncology clinical trial and regulatory communities. Two recent studies (1,2) discussed below illustrate the controversy in relating response rates to survival.

In their study reported in this issue of the Journal, Chen et al. (1) collected information from 21 phase III trials of extensive-stage small-cell lung cancer initiated during the period from 1972 through 1990 and identified those that were preceded by phase II trials of the same regimen. Nine phase II trials were identified. Chen et al. noted that phase II response rates did not correlate with the median survivals of patients treated with the same regimen in subsequent phase III trials. The authors developed a statistical model to assist in selecting chemotherapy regimens from phase II trials for subsequent use in phase III trials. This model used the number of patients, the median survival of patients, and the number of deaths observed in the phase II trials to estimate the statistical power of the subsequent phase III trial. Chen et al. concluded that regimens tested in phase II trials that have an expected power of greater than 0.55 provide a reasonable basis for proceeding with phase III trials.

Buyse et al. (2) also examined the relationship between response rates and survival. In a meta-analysis of 25 randomized trials of fluoropyrimidine therapies in advanced colorectal cancer, the authors noted that an increase in tumor response rate translated into an increase in overall survival for patients with advanced colorectal cancer. Buyse et al. (2) concluded, “tumor response is a meaningful endpoint in testing new treatments for metastatic colorectal cancer because higher response rates predict longer survival, at least for the therapeutic comparisons included in our analyses.”

The above studies used different statistical methods, numbers of patients, and clinical trials. Small-cell lung carcinoma and colorectal cancers have well-known differences in natural history and response to therapies. The divergent findings of the above studies with regard to response rate and survival may be attributed to differences in natural history and therapeutic response, but they may also point to a fundamental debate. If increases in survival are directly attributable to decreases in tumor burden produced by the therapy, then the response rate surrogate is valid. However, if patients who respond to treatment are likely to live longer than nonresponding patients because of other factors, such as better performance status, the surrogate may not be valid. This debate is further exemplified by the flawed concept of comparing the survival durations of responders with those of nonresponders to deduce an improved survival attributed to a therapy (3–5). Patients who survive a sufficient duration to have an opportunity to experience a response will have a predictably longer survival than other patients will, even if the therapy has no effect on survival (4).

Therapies that may provide meaningful therapeutic benefit over existing treatments may be eligible for accelerated approval under the provisions of Subpart H of Part 314 of the Code of Federal Regulations (6). This approval may be granted by the U.S. Food and Drug Administration on the basis of a surrogate end point that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical end point other than survival or irreversible morbidity. Adequate and well-controlled clinical trials are required. Verified objective responses (complete and partial) and meaningful hematologic remissions of sufficient durations have been used as suitable oncology end points under this provision.

Accelerated approval has been used in clinical situations where patients are unresponsive to, or intolerant of, available therapies or where improved patient response over available therapy can be demonstrated. Since March 1996, five new drug applications and two efficacy supplements for new indications have received accelerated approval. Sponsors must commit to perform additional clinical trials that describe the clinical benefit of the agent with “due diligence.” Two agents, irinotecan and docetaxel, that originally received accelerated approval on the demonstration of meaningful response rates have subsequently demonstrated improvement in survival. The remaining agents that received accelerated approval are being tested in ongoing trials to fulfill the clinical benefit commitment.

Complete responses have been used as the basis of traditional approval primarily in hematologic malignancies. Complete response rates were used in the approval of cladribine and pento-

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See “Note” following “References.”
statin for hairy cell leukemia and of ifosfamide (in combination with other cytotoxic agents) for third-line therapy for testicular cancer. In addition, partial response rates have provided sufficient evidence of patient benefit to warrant traditional approval for relatively nontoxic hormonal therapies in breast cancer. Improvement in survival duration in advanced breast cancer trials has generally not been achieved with this class of drugs. Trials leading to the approval of hormonal agents, such as goserelin acetate, anastrozole, and letrozole, for advanced breast cancer were randomized trials with an active control.

Questions regarding the relationship between response rate and survival are increasingly complicated. With novel agents that do not exert their effect through tumor reduction, response rates may be of little value to accurately assess biologic activity and predict clinical benefit. Because second-line and subsequent therapies are used in oncology with increasing frequency, the link between a surrogate end point used early in the disease and the ultimate patient survival may become increasingly strained.

Response rate provides the initial glimmer of antitumor activity in early clinical trials. Survival or time to progression cannot be reliably evaluated in single-arm trials. In certain situations, such as complete responses in leukemia and other hematologic malignancies, the connection between achieving a complete response and clinical benefit, such as reductions in transfusion requirements and infections, is obvious. In other situations, such as first-line treatment of small-cell lung cancer, this connection between tumor response rates and clinical benefit may be questioned. In making clinical and regulatory decisions, the use of response rates and their probability in predicting clinical benefit relies not only on the response rate number but also on the duration of responses, the number of complete responses, the magnitude of increase in this surrogate, and the location of responses (e.g., hepatic versus cutaneous responses). The reproducibility of the response rate in other clinical trials, the history of using this surrogate in predicting clinical benefit for a particular disease setting and drug class, and the integrity and internal consistency of the trial all have an effect on the clinical and regulatory decisions. The relationship of response rate to other surrogates and parameters of clinical benefit (including relief or delay in tumor-related symptoms) may provide a more comprehensive evaluation of the treatment.

Response rate, a piece of the clinical decision-making puzzle, is a puzzle in itself.

REFERENCES


NOTE

The views expressed are the results of independent work and do not necessarily represent the views or findings of the U.S. Food and Drug Administration.