Endpoints for Assessing Drug Activity in Clinical Trials

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ABSTRACT

Overall survival remains the gold standard for the demonstration of clinical benefit. An improvement in overall survival is a direct clinical benefit to patients. An analysis of overall survival requires larger patient numbers and longer follow-up than other endpoints. Survival analysis may be confounded by subsequent therapies. Time to progression usually requires smaller clinical trials and may be more rapidly assessed than trials using overall survival as an endpoint. This endpoint is not confounded by subsequent therapies. Time to progression must use the same evaluation techniques and schedules for all therapies being evaluated. Blinding of trials or the use of an external blinded radiographic review committee is recommended in assessing time to progression. Unlike overall survival and time to progression, which must be evaluated in randomized trials, response rates can be accurately assessed using a single-arm trial. Stable disease is not included in a response rate determination and is optimally evaluated by assessing tumor progression in a randomized trial. Improvement in disease-related symptoms is considered clinical benefit and may be an appropriate endpoint for drug approval. The Oncologist 2008;13(suppl 2):19–21

CURRENT ISSUES IN CONSIDERING CLINICAL TRIAL ENDPOINTS

Regular marketing approval of drugs requires substantial evidence of efficacy derived from adequate and well-controlled trials. The U.S. Food and Drug Administration (FDA) provided guidance documents during the 1980s that indicated that efficacy should be demonstrated by prolongation of life, improved health-related quality of life, or an established surrogate for at least one of these.

In the 1990s, the need to expedite the development and approval of drugs for serious and life-threatening diseases, such as AIDS and cancer, was recognized. In 1992, Subpart H was added to the new drug approval regulations allowing for accelerated approval of drugs for serious and life-threatening diseases where the drug demonstrates an advantage over available therapy. Approval under these accelerated approval regulations is based on a surrogate endpoint reasonably likely to predict clinical benefit. The sponsor must study the drug further to demonstrate clinical benefit in subsequent or ongoing clinical trials. In selecting an endpoint for a trial, sponsors and investigators should discuss with the FDA whether a registration strategy is appropriate for regular or accelerated approval and the optimal clinical trial design [1, 2].

SPECIAL CONSIDERATIONS FOR ONCOLOGY

In the 1970s, the FDA usually approved drugs based on the objective overall response rate (ORR), determined by tumor assessments from radiological tests or physical examinations. After discussions with the Oncologic Drugs Advisory Committee, the FDA determined that cancer drug
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approval should be based on more direct evidence of clinical benefit, such as improvements in overall survival (OS), health-related quality of life, tumor-related symptoms, and/or physical functioning. These benefits may not always be predicted by the assessment of ORR [2].

Several endpoints were subsequently accepted as surrogates for clinical benefit. Improvements in disease-free survival have supported drug approvals in the adjuvant therapy of several malignancies after complete surgical resection of disease. Complete response (CR) rates have led to the regular approval of drugs for the treatment of acute leukemia, because CR of meaningful magnitude and duration is associated with longer OS. A higher CR rate would generally be associated with a lower incidence of infection and use of blood product support. Improvement in tumor-related symptoms in conjunction with a higher ORR with adequate response duration has supported regular approval in several malignancies.

ORR has generally been the primary endpoint for accelerated approvals in selected malignancies. Because the ORR can be directly attributed to the drug administered, single-arm trials can be used to assess ORR in patients with refractory tumors where no available therapy exists.

The following discussion focuses on the FDA’s perspective of the selection of clinical trial endpoints and study designs to optimally demonstrate a convincing effect on these endpoints. Recent workshops held in conjunction with the American Society of Clinical Oncology, American Association for Cancer Research, American Society of Hematology, National Cancer Institute, and FDA have examined both conventional and novel endpoints that may accurately assess the efficacy of cancer drugs.

Traditional Endpoints

OS
OS is the gold standard for demonstrating clinical benefit. Defined as the time from randomization to death, this endpoint is unambiguous and is not subject to investigator interpretation. Survival is a direct clinical benefit to patients, and assessment can be calculated to the day. Patient benefit can be described as superior survival or noninferior survival after consideration of toxicity and the magnitude of benefit. A noninferiority analysis ensures that a survival advantage associated with an approved drug will not be lost with a new agent.

Survival analysis requires a large sample size and may require long follow-up. Survival analysis may be confounded because of subsequent therapies administered after a study drug is discontinued. OS should be evaluated in randomized, controlled trials.

Time to Tumor Progression
Another commonly used clinical trial endpoint, time to tumor progression (TTP), is defined as the time from randomization to time of progressive disease. The progression-free survival (PFS) duration is defined as the time from randomization to objective tumor progression or death. Compared with TTP, PFS may be a preferred regulatory endpoint because it includes death and may correlate better with OS. In TTP analysis, deaths are censored either at the time of death or at an earlier visit. Assessment of either PFS or TTP needs to be conducted in randomized trials. Because of the subjectivity that may be introduced in endpoint assessment, blinding of trials or the use of an external blinded review committee is recommended. In assessing TTP or PFS, patients must be evaluated on a regular basis in all treatment arms, and an assessment of all disease sites should be performed. To reduce bias, the same assessment technique should be used at each follow-up, and the same evaluation schedule should be consistently used.

Prospective discussions with the FDA should specify the magnitude of difference in TTP or PFS that would be considered clinically important. A statistically significant difference in TTP or PFS between treatment arms may not necessarily translate to a clinical benefit for the patient.

ORR
ORR is the portion of patients with a tumor size reduction of a predefined amount for a minimum time period. Response duration is measured from the time of initial response until documented tumor progression.

The FDA has generally defined ORR as the sum of partial responses (PRs) and CRs. When defined in this manner, ORR is a direct measure of the drug’s antitumor activity. Stable disease is not included in the ORR. Stable disease is optimally evaluated in randomized trials examining TTP or PFS. Stable disease may reflect, in part, the natural history of the disease rather than being entirely attributed to the drug’s therapeutic effect.

Several response criteria have been considered appropriate to evaluate antitumor response. The selected response criteria to be used in registration trials should be prospectively discussed with the FDA. When comparing ORRs in different arms, the number of PRs and CRs, response durations, locations of responses, and associations between responses and symptom improvement should be examined. The clinical significance of the ORR should be assessed by the magnitude and duration in a risk-benefit analysis.

Time to Treatment Failure
Time to treatment failure (TTF) is defined as the time from randomization to treatment discontinuation for any
reason, including disease progression, treatment toxicity, patient preference, or death. From a regulatory point of view, TTF is generally not accepted as a valid endpoint. TTF is a composite endpoint influenced by factors unrelated to efficacy. Discontinuation may be a result of toxicity, patient preference, or a physician’s reluctance to continue therapy. These factors are not a direct assessment of the effectiveness of a drug.

**Patient-Reported Outcomes**

Symptomatic improvement is considered a direct clinical benefit and may be an appropriate endpoint for regular approval. FDA drug approvals have used patient symptom assessments and/or physical signs representing symptomatic improvement as primary efficacy endpoints. Measures of health-related quality of life have not yet served as primary efficacy endpoints for oncology drug approvals. Improvement in signs or symptoms must clearly distinguish between tumor symptoms and drug toxicity. Patient-reported outcomes are optimally evaluated in randomized, blinded trials.

**Conclusions**

Selection of endpoints for trials for regulatory purposes should be discussed with the FDA prior to the initiation of the clinical trial. The endpoint should accurately assess the efficacy of the drug being evaluated, and the endpoint and the trial design should minimize potential bias.

Although the demonstration of longer OS may be considered a preferred regulatory endpoint, the use of this endpoint has limitations. In disease settings where limited accrual to trials is anticipated, drugs have been approved on the basis of response rates or the demonstration of a longer TTP or PFS duration in randomized trials. The approval of imatinib for the treatment of gastrointestinal stromal tumors (GISTs) was based on the demonstration of a higher ORR. The subsequent approval of sunitinib for the treatment of GIST after disease progression or intolerance to imatinib was based on a longer TTP. That randomized trial allocated 207 patients (2:1) to either sunitinib or placebo. An interim analysis of efficacy and safety after 149 progression events demonstrated highly significant findings for both TTP and PFS. The use of these endpoints also allows patients to cross over to receive active therapies without confounding the interpretation of the TTP or PFS endpoints.

In rare diseases where randomized trials cannot be performed because of very limited populations, the FDA has approved indications on the basis of single-arm studies supported by data from the published literature. In 2006, imatinib was granted approval for the treatment of dermatofibrosarcoma protuberans (18 patients), myeloproliferative/myelodysplastic syndrome (31 patients), aggressive mastocytosis (38 patients), and hypereosinophilic syndrome/chronic eosinophilic leukemia (176 patients).

Different endpoints may be appropriate depending on the type of regulatory approval being considered. The magnitude of the effect demonstrated on the selected endpoint is considered in an overall assessment of a risk-benefit analysis to determine whether marketing authorization will be granted.

**References**