Trends-in-Medicine

May 2004
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Quick Pulse

Trends-in-Medicine
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FDA Oncologic Drugs Advisory Committee (ODAC) Meeting on Clinical Trial Endpoints in Colorectal Cancer (CRC)

Gaithersburg, MD
May 4, 2004

The FDA has been working for more than a year on updating clinical trial endpoint requirements in a variety of different cancer trials. The agency is expected to put out general guidelines later this year for public comment. Soon after, FDA officials hope to have draft guidelines for lung cancer and then colorectal cancer.

The colorectal endpoint guidelines took a step forward at the ODAC panel on May 4, 2004. Following several meetings, workshops, and discussions on the topic, the FDA asked ODAC to vote on several issues. The panel:

- Recommended that the FDA allow disease-free survival (DFS) to be used as the primary endpoint for regular drug approval in CRC, based on a minimum of three-year follow-up.
- Advised that progression-free survival (PFS) is a better endpoint than time-to-progression (TTP).
- Was divided on whether PFS could be used for approval of a drug for first-line treatment of advanced CRC.
- Believes that showing no survival decrement is important, but a survival benefit is not necessary.

Prior to the votes, an FDA official reviewed the regulatory background in CRC approvals, and other experts reviewed the discussions at previous FDA meetings and workshops on CRC endpoints.

A statistician from AstraZeneca argued in favor of adoption of PFS in first-line CRC. He said a review of three CRC trials by his company found that progression is a meaningful endpoint by itself in CRC. He concluded, "Progression is a meaningful endpoint in first-line CRC…and should be employed as a primary endpoint in clinical trials."

Currently-Approved CRC Agents

Measurement	Adjuvant	First-Line	Refractory
Approved CRC agents	Levamisole (+5FU)	Leucovorin (with 5FU) Irinotecan (+5FU/LV) Capecitabine Oxaliplatin (+5FU/LV) Bevacizumab	Irinotecan Oxaliplatin Cetuximab
Basis of approval	Superiority in survival	Superiority in survival (4) Non-inferiority in survival (1)	Survival (1) RR and/or TTP

The FDA posed these questions to the panel:

QUESTION 1A: For a colon cancer drug, could an increase in DFS compared to standard therapy represent clinical benefit and be an adequate basis for regular drug approval?
Vote: Yes by unanimous vote (15-0)

QUESTION 1B : What duration of DFS follow-up is needed before evaluating DFS for regular approval – three years or five years?
No vote, but the FDA acknowledged that the panel was recommending a three-year minimum follow-up.

A panel member said, "Three years…seems more sensible…and leave it open to alternative durations." A panel statistician said, "Three years seems reasonable as a minimum – or at least three years on enough patients." A Kansas oncologist said, "It can't be just three years from the start. It has to be three years from a fixed date."

QUESTION 2: When a surrogate endpoint for clinical benefit is needed in advanced colon cancer, would the preferred endpoint be PFS or TTP?
Vote: Unanimously recommended PFS (15-0)

However, panel members strongly recommended that the FDA define PFS. An FDA official responded, "We are definitely working on that internally, and we will have external discussion/comments. We think it needs a lot more work." Another FDA official said, "We've outlined some problems that need to be put forward not only in guidance but in the prospective plan that the company writes, which may be different from one drug to another. This includes what to do if a patient misses an appointment, how to handle the review committee, etc. In CRC we may just want to look at a radiology review since most people don't have physical

Issues in CRC Trial Design

Measurement	Advantages	Issues/Disadvantages
Biomarkers or quality of life (QOL)	Clinical benefit response (CBR)	1. CBR does not adequately encompass symptoms experienced by patients 2. Methodological issues in assessment 3. Not useful if asymptomatic
Surrogate endpoints	FDA has granted approval using surrogate endpoints not formally validated	1. May reflect biological activity without establishing clinical efficacy 2. Meta-analyses required to validate 3. Validated surrogate endpoints are rare
Non-inferiority trials		1. Insufficient for curves to overlap 2. Conservative margins needed to exclude significant decrease in efficacy 3. Rigorous study conduct needed to avoid incorrect conclusion of non-inferiority 4. Will the results move the field forward?
TTP in metastatic CRC	1. Directly evaluates changes in disease burden 2. Correlates with other outcomes (e.g., survival) 3. Not confounded by subsequent therapies 4. Offers utility as an endpoint in non-inferiority trials (more rapid completion)	Evaluation of symptoms is problematic because progression frequently is not symptomatic, is subjective, and is difficult to measure
3-year Disease-free survival (DFS)	1. Seems to be excellent predictor of 5-year overall survival 2. Event rates virtually identical (no impact on sample size) 3. May slightly overestimate differences in 5-year OS 4. Used for full approval in breast cancer adjuvant therapy 5. Would allow more rapid trial completion	1. Not a formally validated surrogate 2. Does improvement represent clinical benefit in its own right?
PFS/TTP in first-line disease	1. Not obscured by crossover 2. Tumor progression is in the direct path of morbidity and death 3. Smaller studies needed to detect a difference in survival	1. Most colon cancer patients are not symptomatic at time of initial progression 2. Not validated as surrogate for survival 3. Indirect measure of patient benefit 4. Clinical meaning of small PFS/TTP difference is unclear 5. Cannot be measured with the same accuracy as survival 6. Reliability in an unblinded setting has been questioned
Progression-free survival (PFS)	1. Deaths are included in analysis, so unanticipated drug effects on survival would be included 2. Avoids censoring of deaths (as occurs with TTP)	1. Composite endpoint. Progression and death are not equal events but are treated as such. 2. PFS estimate will be prolonged when deaths are counted as events in patients without adequate tumor follow-up 3. Including unrelated deaths may decrease the statistical power of the study 4. TTP may be a more appropriate endpoint where most deaths are due to natural causes

symptoms…We are talking internally about how to review x-rays, how many to review (audit), and including radiologists as investigators…That (including radiologists) has to be done because the reports have to have uniform meaning. We can't get vague reports. There has to be identification of a radiologist at each site and adequate resources directed at that individual."

QUESTION 3: For approval of drugs for first-line treatment of advanced colon cancer, could a PFS/TTP benefit of a new drug compared to a standard first-line regimen justify regular drug approval – assuming the standard control arm has a known small (2 month) survival benefit?
Mixed Vote: 8 Yes, 5 No

The panel thought the FDA should be flexible on the magnitude of PFS improvement that is clinically relevant, but that it should be substantial (months, not days or weeks).

QUESTION 4A: Should trials rule out a survival decrement of some size?
Recommendation: Yes, that is reasonable.

QUESTION 4A: 4B: Should trials be powered to detect a realistic improvement in survival even if survival improvement is not an approval requirement?
Recommendation: No, requiring a trial to be powered for survival may be too great a burden for a sponsor. ♦