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by Lynne Peterson

SUMMARY

This was only the first step in an effort to revise acceptable endpoints in colorectal cancer trials, and no decisions were made. An industry rep made a plea for acceptance of time to progression (TTP) as an endpoint, saying it is objective, reliable, practical and cost saving. However, the FDA does not appear ready yet to accept TTP endpoints, which are still con-sidered difficult to interpret. The FDA also is not enthusiastic about non-inferiority survival trials in first-line, second-line or refractory settings because they don't move the field ahead, and problems arise due to sloppiness, crossovers, lack of confirm-atory trials, etc. Single-arm studies are being allowed for approval before a randomized trial is completed, and that is unlikely to change in the near future. Bio-markers and quality of life will be useful endpoints eventually, but they are not ready for prime time yet.

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FDA Colon Cancer Workshop

November 12, 2003
Washington, D.C.

This was a planning meeting, a workshop, not a session for experts to give advice to the FDA. The goal was to gather information on the pros and cons of endpoints used in colorectal cancer trials, to identify speakers the FDA might invite to meetings in the future where the Oncology Drug Advisory Committee (ODAC) might discuss and vote on adopting new endpoints. This workshop discussed – but didn't vote on – a number of endpoint questions discussed below.

Dr. Richard Pazdur, Director of Oncology Drug Products (DODP) for the FDA, said, "For many years, as a GI oncologist, I heard the mantra that there is nothing better than 5FU...but, low and behold, the landscape has changed. We have new drugs and drugs in the pipeline that have changed that mantra, so it is important to look at the endpoints that we have traditionally used."

Grant Williams, Deputy Director of DODP, provided an overview of the current regulatory situation. He pointed out that FDA requirements for approval are safety and efficacy in adequate and well-controlled studies – with an emphasis on the plural, *studies*. Standard clinical endpoints are: survival and improvement in tumor-related symptoms, not response rate. He commented, "Sometimes FDA has accepted surrogates, usually after much experience with it and widespread acceptance by the medical community…but sometimes that has proven wrong, such as the benefit of suppressing some arrhythmias."

An FDA review of drugs approved since 1990 found that only 27% of regular approvals were based on survival, and 33% of accelerated approvals were based on on survival.

Endpoint	Number approved
Survival	18
Response	26
Disease-free survival (DFS)	2
Time to progression (TTP)	1
Recurrence of malignant pleural effusion	2
Recurrence of breast cancer	2

Drugs Approved for Relief of Tumor-Related Symptoms

Drug	Symptom Relief
Mitoxantrone (Immunex's Novantrone)	Pain
Bisphosphenates	Skeletal morbidity scale
Daunorubicin (NeXtar Pharmaceuticals' DaunoXome)	Visible lesions of Kaposi's sarcoma
Porfimer sodium (Sanofi's Photofrin)	Dysphagia scale

Accelerated approval can be granted for drugs to treat a serious or life-threatening disease can be based on a surrogate endpoint that "is only reasonably likely to predict clinical benefit." However, post-marketing studies must verify clinical benefit…If those studies fail or are not diligently done, the law allows for accelerated withdrawal of the product, though officials said that is extremely difficult to do.

Accelerated approvals require:

- Substantial evidence from well-controlled trials. Borderline evidence is not acceptable.
- Benefit over available therapy. An official said, "To meet this, most sponsors have established single-arm trials…but because there is no control, they can evaluate only very few interpretable endpoints."
- Use of a "reasonably likely surrogate."

THE INDUSTRY PERSPECTIVE

Dr. Langdon Miller, Chief Medical Officer of PTC Therapeutics (a former Pfizer official), made a plea on behalf of industry for acceptance of time to progression (TTP) as an endpoint in colorectal (CRC) trials. He said, "Prolonged survival has served to increase sample sizes, prolong accrual times, delay analysis, and increase cost…For a non-inferiority survival study, the sample size and length become even more extreme…At $40,000 per patient, the total cost of survival studies (with cytotoxic agents) could reach stratospheric heights…Survival superiority studies today offer too little, too late and for too much."

There are many reasons not to use symptom control as an endpoint, Dr .Miller insisted. He said, "The use of symptoms creates problems with complexity, subjectivity, reliability and interpretability, making study design and analysis difficult." Among the issues he cited in using symptom control as endpoints were:

- Subjectivity of symptom severity
- Disparate types of symptoms that complicate inter-pretation.
- Missed symptoms.
- Lack of collection instrument sensitivity to changes in tumor size.
- Subjective measure of quality of life (QOL) may not change despite changes in tumor size.

Time-to-symptom-progression also is not useful, Dr. Miller said, because it usually occurs substantially later than tumor progression. He commented, "Declines in symptom scores and function scores most often occur after tumor progression…So how would we analyze progression when the patient is off study and is receiving second-line therapy?…That would confound the results."

His contention was that TTP offers an objective, reliable and practical alternative that "represents the most common cause of treatment failure, incorporates the value of time, and allows direct assessment of disease burden in a way that logically correlates with survival…Tumor progression is the most common cause of CRC cessation of therapy…TTP better categorizes tumor control than response rate does…It is only logical that halting tumor progression is beneficial…TTP actually does correlate with survival in metastatic CRC." He also claimed that TTP:

- Provides a direct reflection of drug activity
- Is not confounded by subsequent therapies
- Speeds time until final analysis
- Reduces sample sizes
- Shortens accrual time
- Deceases cost
- Is based on simple, standardized radiographic tumor measurement criteria
- Can be subjected to blinded review

He presented a hypothesis that survival = 1xTTP+9 months, with a near 1:1 correlation between TTP and survival. He said this relationship is constant independent of treatment, performance status or baseline LDH. He presented an analysis of some Pfizer studies to support this hypothesis.

The caveats he noted in assessing TTP included:

- Minimum intervals between tumor assessments should be less than the expected treatment effect size.
- Tumor assessment frequency should be the same across different arms or there can be an increase in false positives.
- Conservative censoring rules should limit TTP to time-on-study therapy to avoid bias that causes artifactal prolongation of TTP and to avoid situations where the higher the dropout rate, the better the TTP.

A STATISTICIAN'S VIEW OF DESIGN ISSUES IN CRC TRIALS

Dr. Thomas Fleming, a statisician at the University of Washington who often advises the FDA, contended that TTP and biomarkers (e.g., CEA) are surrogate endpoints that can be difficult to interpret and can lead to false conclusions. Some of the problems he cited were:

- **The disease process often has several pathways** by which it affects clinical outcome, which can result in false positives or false negatives.
- **A drug could have an unexpected or unintended effect**. For example, a cardiac study found suppression of arrhythmias supposedly had an effect on survival but actually tripled the death rate.
- **A valid surrogate must be correlated with clinical outcome**. Dr. Fleming said, "This is a major misunderstanding…A marker may be correlated with

clinical outcome…and that is important…but it is not sufficient…A surrogate must fully capture the net effect of treatment on outcome."

- **Non-inferiority trials can lead to "bio-creep**." For instance, drug B might be shown to be non-inferior to drug A, and then drug C to be non-inferior to drug B, but that doesn't necessarily mean Drug C is non-inferior to Drug A. Dr. Fleming said, "The challenge arises if you want to base (non-inferiority) approvals on TTP. This is my worst nightmare – not a TTP surrogate endpoint." Dr. Pazdur added, "If you think that is your worst nightmare, consider a trial about non-inferiority with surrogate endpoints and a substantial amount of crossover."
- **In non-inferiority trials, it is not enough for the curves to be overlapping.** And for a superiority trial, separation of curves is not enough.

THE PANEL PERSPECTIVE

Panel members found Dr. Miller's argument interesting, but they wanted additional data to support it, perhaps from existing trials in large databases. A statistician from the Mayo Clinic wondered, "There is data out there, but it is institutional or cooperative group data that hasn't been reviewed, so can it be accepted?" Dr. Pazdur suggested, "Maybe we want to look at cooperative group and other database."

Pro use of TTP:

- Industry: "It is just common sense that having a tumor progress is a bad thing and…no tumor at all is a very good thing…We say a drug has failed when a patient progresses…The inverse is that a drug is successful as long as the patient doesn't progress."
- Oncologist: "The breast cancer world has moved toward more use of TTP…The breast cancer data suggest they haven't been burned yet with TTP…Their groundwork has held up so far…I don't want to be held to a different standard than other diseases."
- Former ODAC member: "What is important to patients is that they are doing well…If a lump is small or stable or if a lump goes down, perhaps quality of life is better as a result…In colorectal cancer we deal with a lot of patients who are asymptomatic…so it is important what patients feel like." He noted that there is a wide range of interpretations of TTP but survival is a hard endpoint.

Con use of TTP:

- "In oncology, studies tend to be smaller than in other therapeutic areas…so standard errors are larger."
- Statistician: "The cardiologists would have said it is common sense that suppressing arrhythmias is a good thing…but they did that with (a drug), and it tripled the death rate…It is common sense that with blocked arteries, you want to achieve patency…but the issue is how quickly, at what level, to how many people, and do you achieve it without unintended effects…Many times what seems clinical common sense is not a basis for a reliable surrogate."

PANEL DISCUSSION OF FDA QUESTIONS

The FDA posed a series of questions to the panel. They discussed these, without voting, including:

Question 1: Is survival the only acceptable endpoint for supporting the approval of drugs for first-line treatment of CRC? (*Or, is TTP an acceptable alternative.)* **Mixed opinions.**

Dr. Pazdur wondered: "If a drug has a significant impact (20%-25%) on survival, and we get an application for another drug that shows efficacy and safety but perhaps has a lower level of a survival impact, should we approve that? It is safe and effective, and the law doesn't say it has to be safer and more effective."

Yes, only survival is acceptable:

- "Yes, because it is the only hard endpoint…With TTP you have to listen to a variety of things to sort out whether they are related to disease…X-rays are hard data, but they have to be read right…And survival in most people equals quality (of life) in some way."
- Dr. Pazdur: "If we never ask about survival, we will never know the true gains of our therapy, which may affect the robustness of drug reimbursement, etc…We've had underpowered trials coming in...and I have a great fear that if we just power for TTP, we will be on a slippery slope here and have underpowered trials for TTP even."

No, TTP could be used in lieu of survival:

- "No. Survival is verifiable, and TTP is not easily…but (better) imaging technology is being developed…I'm not persuaded at all that only survival should be the endpoint…Looking retrospectively at databases will tell us if TTP is valid or not…(but) we may need independent review bodies."
- "If TTP is not acceptable, why do we use it…We operate under the assumption that TTP is a first readout on the causal pathway…We accept toxicity and a drop in quality of life; we don't accept progression of disease."
- Patient advocate: "One of the problems with TTP is we don't have enough information about it…I've talked to enough radiologists to see on both an anecdotal and a trial basis, that it is not black and white."
- "If TTP reliably predicted survival, then it would be an acceptable surrogate…but whether TTP in and of itself is a benefit, you need to consider the patient population…I am willing to accept that TTP could be a surrogate for accelerated approval, but I'm not convinced that TTP -- in asymptomatic patients – represents a benefit to patients."

Interpretation of the data is a key issue with use of TTP as an endpoint. An FDA official said, "There will be a lot of temptation to interpret TTP in a favorable way." Another FDA official said, "At some point in progression, we all generally agree that it means a drug is not working…You can agree that you should stop a drug at a certain PsA or progression and not be convinced that the endpoint provided a quantitative ability to evaluate the drug." An oncologist said, "Many investigators are accepting a radiologist's reading, and they shouldn't…Even among cooperative group trials or industry trials there are different standards…Industry trials generally go to a group of radiologists who are asked to do this blindly without knowing the arm…In a cooperative group generally we are not blinded, so there is all this bias in TTP."

One suggestion was a core lab to read TTP x-rays. Dr. Pazdur said, "We have a lack of blinding in oncology which can tremendously impact even an expert panel." A panel member said, "I don't think it is that much of a problem…There are CROs who do this as a living -- in a blinded fashion with radiologists and oncologists present – so it seems to me possible." Another panel member disagreed, "Even expert panels have difficulties…Imaging experts are spending a lot of time trying to standardize criteria to clarify progression, especially in asymptomatic patients."

Proposed TTP Approval Strategy

TTP	Toxicity	Survival
A > B	A ≤ B	A ≥ B
A=B	A ≥ B	A ≥ B

Question 2: Is a demonstration of non-inferiority with respect to survival a viable approach for drug approval in this setting, or are the difficulties too great (e.g., the small and imprecisely defined survival benefits associated with standard therapy)? If this is a viable approach, suggest active control treatments for these studies. Generally negative opinions due to problems with sloppiness, crossovers, etc., that can confound results.

A statistician's view: "I need an active comparator with a very substantial level of efficacy that can be precisely estimated…Many times it is estimated enough just to achieve statistical significance, and that is not enough…And it gets worse…You have to know the study is done with high quality on adherence, data capture, etc…In a superiority study if you have noisy factors, it leads to dilution to null…but in a non-inferiority trial, you get the appearance of equivalence when it isn't real…It becomes extremely complex to do a non-inferiority study…We need much higher standards for overall quality. I'm not persuaded that it always means a larger sample size…We need to know more than the median survival on an active comparator…I have to know the active comparator vs. placebo…We discussed challenges of non-inferiority trial…and it was suggested we could use TTP…but if that is being done where TTP is viewed as not a true clinical endpoint or a valid surrogate, then I reiterate that this is my worst nightmare…You in essence still in the end need to conclude that a drug is not inferior to the comparator relative to a clinical endpoint, and now you have the added challenge of saying how much worse can I be in TTP and not be worse in survival?…So, it is a more complicated design."

The FDA perspective. Dr. Pazdur said, "I'm concerned with the amount of time we spend at the agency discussing non-inferiority trials…I realize from a risk reduction perspective that it is easier for industry...and reducing toxicity is a laudable issue…but when we have a preoccupation with son of this, daughter of that, taxol-free this, liposomal encapsulated this and that, I feel we are not capturing the prize and investing resources as they should be. It can become excessive."

Dr. Pazdur pointed out several issues relating to non-inferiority trials:

1. **Sloppiness is rewarded in non-inferiority trials.** "If you do a sloppy trial, the control can lose the treatment effect, and so you are approving a placebo potentially…When we ask for two trials, we are not being heavy-handed."
2. **Crossovers can confound the results.** "If there is crossover in a non-inferiority trial with a survival endpoint, what do we do then? It is exceedingly messy to deal with that…It may not be an issue with an NME (new molecular entity), but for a supplement already on the market, we firmly believe people will cross over. The drug is there." A statistician said, "Crossovers really do complicate our analysis...When you censor them, you are still leaving them in the trial...unless the crossover was truly random…but it is not a random crossover, and I can't correct it by censoring…Why is it so necessary to cross over?…Why not find out what you care about instead of crossing over?…We could possibly look at survival at an earlier point in time. Rather than log rank over all time, may be we could look at one-year survival, not censoring for cross-overs."
3. **Approval might have to be based on one TTP trial.** "We can allow a second trial in an earlier stage of disease…where a more powerful impact is expected...but that presents problems…If you want to use data for non-inferiority, then we are stuck with only one trial with a TTP endpoint…It is rare where people will go back and do more trials after approval."

In favor of non-inferiority trials:

- "It appears that TTP may have implications for future exposure to other agents that will then impact on overall survival...so it is almost looking ahead to what benefit people will have over time...From 2000 to 2003, we went from 14 months to 21 month survival, and that appears due to integration of most of these regimens that showed a TTP benefit…so two TTP trials should give an element of comfort."

Against non-inferiority trials:

➢ "I'm very suspicious of non-inferiority trials...I'm not sure they are worth the effort."

➢ "It is very difficult to do survival non-inferiority in this disease…With the number of therapies available, how would you set a sample size?"

➢ "A sponsor is nuts to design a non-inferiority trial…It doesn't move the field forward. It is enormously complicated and expensive…You can always define a comparator at any time, but by the time you have the results of the trial – even if you have a locked agreement with FDA – will anyone care any longer? The risk for the sponsor has to be enormous to take this path, and I can't see why anyone wants to do it...And then, if two trials are required, it makes it an extraordinarily risky and foolhardy decision."

➢ "Avastin (Genentech, bevacizumab) is coming forward…and we said survival (in CRC) was 20 months, and now (with Avastin) it isn't."

Question 3: For superiority, in a design where Drug B beats Drug A, what control arms are ethically and practically acceptable for evaluating survival in the first-line treatment setting? Companies have been submitting a single-arm trial while a randomized trial is underway, and the FDA has concerns with this, but the panel had no simple alternative.

➢ Oncologist: "I was thinking that the initial study design would be powered around TTP but with important additional collection of survival data that would become a more descriptive analysis of what happens to people...and if the curves are falling out to be roughly the same in survival, then that is adequate support of initial acceptance of TTP, enabling us to learn as we go…but it does require stricter criteria on approval and withdrawal…which is hard to do...How do you withdraw a medication that patients are on and benefiting from if the confirmatory data is not there?"

➢ Statistician: "My worry is that overlapping survival curves could be consistent with a lot worse survival…There has been a lot of discussion within the FDA across divisions on this…That to replicate the first study would be ethically-challenging…Where the endpoint is compelling -- like survival, prevention of transmission of HIV, prevention of stroke, or prevention of loss of sight -- my sense is there has been some accommodation…Where the agency said if there is a single trial, and the results are robust and compelling, the agency stopped short of specifying a p-value, because it depends on setting – like cardiovascular toxicity showing up with Herceptin…It makes sense to allow more lenient criteria with survival...but it is a big risk to plan a trial with a p-value of 0.025…because then you better hope no irregularities come up…Xigris (Lilly, drotrecogin alpha) was approved on a single study, but with irregularities that led to complications and a split advisory committee vote."

➢ The FDA's Dr. Pazdur: "There are many hard liners in the agency who demand greater statistical persuasiveness than with one trial…What about accelerated approval of an interim analysis based on TTP and then follow that with a survival study? Then, what do we do if the drug fails the survival study?…Oxaliplatin (Sanofi's Eloxatin) did not show a survival benefit after we approved it, but we are comfortable with it, and that is not a problem for us…There is still this love affair (with accelerated approval), and a lot of it has to do with risk reduction in oncology…A 'Lets get a smaller response rate and get the drug approved' strategy…If that is the only strategy, it leaves us with a difficult situation and may be short-changing the drug…A drug that should be approved won't be because we will study it in a refractory disease setting where the response rate will be so low that we can't make heads or tails of it…What many sponsors have been doing to manage risk in oncology drugs – and the FDA recognizes this is a risky area in drug development -- is submit a single arm study but have a randomized study that is actively accruing…This has several advantages...If the company wins, it can get accelerated approval, but if we still want to wait, they have a second chance with the randomized trial…But we are spending a tremendous effort calling back sponsors."

➢ Another oncologist: "In first line, TTP saves time. In second-line therapy, time from TTP to survival is shorter, and one could argue, let's look at everything (including survival)…If TTP is a true clinical benefit or a valid surrogate, then why are we talking about accelerated approval...we should be talking about full approval."

➢ A third oncologist: "If we did accelerated approval front-line, there is another opportunity for bio-creep…We could end up quickly down the bio-creep pathway and end up going down the wrong direction."

➢ Another statistician: "Even if we were to accept TTP as a validated surrogate for cytotoxic agents…the whole issue starts again when we talk about biologics…Surrogacy includes a mechanism of action, and the assumption for a true surrogate is that the surrogate endpoint captures the entire mechanism of action of the agent on the ultimate endpoint…You may feel somewhat comfortable with that for cytotoxic agents, but it is a different question for biologics…Censoring issues can be very tricky for non-cytotoxic drugs in terms of when a patient is on therapy and hasn't progressed and stopped therapy...We can't assume the benefit of the agent stops…It may be that you give therapy until you achieve a sufficient response, and then the patient may continue in response for considerable time and to censor at that time point is not accurate."

➢ FDA official: "The data that is actually reviewed by us quite a lot of time leaves something to be desired on TTP."

Question 4: In second-line, could prolongation of TTP in a randomized study be sufficient for regular approval? If not, could prolongation of TTP in a randomized study be

sufficient for accelerated approval? No. Survival is too short for TTP to be useful in second line CRC.

The FDA's Dr. Pazdur wondered: "If disease progression shortly precedes death – if there is a small difference between radiographic progression and demise – is the trade off in surrogates or inaccuracies of TTP worth it?"

The variability of TTP is compounded by reading errors, panel members agreed. A statistician said, "It is pretty clear that an independent assessment drops the response rate by about 10%." An oncologist said, "We've seen the same thing with our audits…I've been led to believe that we are going to be wrong at least in a certain percentage of cases, but there is no impact on the trial…But I haven't seen a comparison linking audit findings with the overall outcome of a study." Another oncologist said: "We just did an ECOG audit…and we reviewed something we had to reverse about one time out of ten…It is about a 10% change…And the audit team is only auditing 10% of the accrual...so it is 10% of 10%."

- Oncologist: "My opinion is these people are more likely to have symptomatic progression."

- Industry rep: "Second line doesn't last long in this disease."

- Statistician: "If there is a short setting from TTP to death, I would argue that TTP is not as relevant…If the progression cascade moves quickly, the timing of the measurements may be more important…and is that a setting where you really are capturing all of the impact?…Is the demise caused strictly by growth of the measured tumor or are there other multi-organ things going on that are not reflected in TTP but would be (reflected) in overall survival."

- The FDA's Dr. Williams: "We don't necessarily have to do a full confirmatory trial in the same setting…There are ways to get a confirmatory trial done." Dr. Pazdur added, "If the trial doesn't show a survival advantage, that doesn't mean the therapy doesn't have a survival advantage – just that you failed to show it...You have to be cognizant of crossovers, etc."

Question 5: Could a superior response rate in a randomized study support accelerated approval? No.

Dr. Pazdur said, "We have traditionally looked at response rate and TTP as reasonably likely to predict a benefit…The issue is: With the response to CPT-11, we have had a love affair with response rates…Medical oncologists like them… They get immediate gratification with them…Whereas, TTP and survival tend to be abstract concepts in the clinic. In a single arm trial, could we be putting too much emphasis and even missing drugs?…CPT-11 had a 15% PR and yet went on to demonstrate in two trials a survival advantage, and one would not have intuitively expected a 15% OR would impact overall survival…Did we miss something with that drug? Should we have gotten the European data?"

An oncologist said, "The standard dose of CPT-11 is probably the wrong dose for most patients…The average dose for the population is often the wrong dose for an individual patient…I think I hear you saying we shouldn't rely exclusively on response rate."

Statistician: "We may be achieving a clinical benefit in terms of magnitude and duration...but that may not capture full clinical benefit."

Question 6: Are there any reservations about non-inferiority trial in the refractory setting? Yes.
Oncologist: "Yes, this is a different patient population, a sicker population…When they progress, there is a higher likelihood they won't live much longer…and quality of life during the refractory stage is important…It is hard to compare two toxicities…I'd rather have Grade 3 hypertension instead of Grade 3 neuropathy, but both are Grade 3."

A second oncologist: "We have the example of CPT-11, and we know its survival advantage…If someone is trying to bring forward a new drug with non-inferiority to CPT-11, and there was no diarrhea, you could go to the patient and say, 'I could give you CPT-11, which prolongs survival three months but has significant diarrhea, or I can give you Drug X which prolongs survival 1.5 months and has no diarrhea. Which do you want?'"

A third oncologist: "It looks like we are moving toward a question of a change of criteria for second-line and third-line approval, which would be a swamp – a mixture of not-yet-validated TTP, not-yet-validated quality of life, and response rate, which we all agree is not very reliable…And talking about a composite score of three more or less weak, or not-so-weak data, and making that criteria….What makes me uncomfortable is that we don't have data on TTP, we don't have great data on quality of life, and performance status is in the eye of the beholder…Are you proposing a composite analysis?"

Question 7: How reliable are biomarkers and quality of life endpoints? They will be used in the future, but they are not ready yet.

BIOMARKERS

A panel member explained that CEA, a glycoprotein member of the immunoglobulin gene superfamily, is elevated in a number of inflammatory diseases and malignancies, and he said it is a promising marker, but he does not think it is ready for prime time. Among the points he made were:

- "ASCO recommends CES as the marker of choice of monitoring CRC, but at present the data are insufficient to use

it alone to monitor patients…ASCO recommends using a variety of markers in monitoring treatment of CRC.

- "CEA has only about a 53% positive predictive value, but it negative predictive value is good -- 100%…This means, you can have a CEA response without a true ORR, but you can't have a true ORR without a CEA response…CEA response correlates with survival even in the absence of ORR.
- "You can progress without CEA progression…but you cannot have CEA progression without x-ray progressive disease.
- "CEA progression may occur months before any change on CT…X-ray progressive disease without CEA progressive disease is particularly common with growth of anaplastic tumor clones.
- "CEA and all markers overestimate responses and underestimate progressive disease.

Another oncologist said, "Most oncologists won't use CEA…but it is a warning sign and might help tighten therapy."

The FDA's Dr. Pazdur said: "The agency has been in tremendous discussions about use of other biomarkers in other diseases – such as PSA in prostate, etc…What should their use be in disease progression? I have not heard from oncologists about CEA. Why? Because we have fairly measurable disease patients."

Quality of Life

A panel member said, "Palliative chemotherapy may not truly improve quality of life. A meta-analysis of 13 trials found mixed results…Some showed better quality of life with palliative chemotherapy, some showed no difference, and one found quality of life worse with chemotherapy (but that was ineffective chemotherapy)…Data on quality of life is insufficient to draw conclusions in CRC…I suggest if we go down this path, we may want to use clinical benefit response, which worked for gemcitabine in pancreatic cancer."

Among the problems with quality of life assessments in CRC are:

1. Missing data.
2. Questions that are not agent/toxicity specific/sensitive.
3. Patient variability in filing out quality of life forms/questionnaires.
4. Composite scores that may not be sensitive enough to differentiate progression from chemo toxicity.
5. Timing.
6. May not take into account all disease-related symptoms of importance.
7. Difficulty in developing a CRC-specific questionnaire.
8. Asymptomatic patients.
9. Lack of consistency in terminology used to discuss specific symptoms.
10. Clinical significance of an improvement depending on the magnitude of change but also the severity of symptoms at the start.
11. No good research definition for what counts as symptom "control."
12. Lack of blinded trials.
13. Medical oncologists' ability to assess symptom benefit.

Panel members offered several interesting comments on this topic, including:

- "More and more second and third line patients will be symptomatic…Most people want quality of life with less toxicity...Is toxicity assessment alone sufficient or should we be incorporating quality of life instruments that passed the test of time to help make these decisions?"

- "The biggest single problem we see in clinical trials is a lack of pre-specified hypotheses on quality of life outcomes. The typical clinical trial is designed with a hypotheses of a treatment effect, and then quality of life data is layered on top with no specified hypothesis as to what the primary quality of life endpoint is, the magnitude of change expected, the sample size required to detect that…So, at the end of day, we don't have any information that is interpretable." Another oncologist said this is starting to change, "ECOG is starting to look at that, so that will change…Quality of life is important, but we need simpler and better ways (to measure it), and ECOG is working on that."

- "Patients develop symptoms later in CRC than in pancreatic cancer…Maybe this is the wrong place to put resources in CRC…Maybe we should look at biomarkers and imaging."

- FDA's Dr. Pazdur: "At the end of the day, we need to be sure it is a real drug, the data is reliable, and that we are not missing data…Why are we looking at this vs. other endpoints? Is it a different population, a more symptomatic population? Once patients start developing symptoms, it may not be the optimal situation (to measure quality of life)?"

- Industry rep: "Quality of life assessments are expensive to do…So, the concerned from the sponsor perspective is that they will be trying to evaluate subjective, loose data that costs a lot of money to collect, and the risk goes up substantially because they won't have anything at the end."

- Patient advocate: "As we sequence treatments and put people on more and more treatments…the quality of life issues become more important…I spoke with a large number of patients before this meeting, and there wasn't one clear answer…People with kids cared about quantity – they wanted to see a grandchild get out of high school, go to a wedding, etc. Others, who didn't want to be sick, wanted to enjoy the time they had left…In small trials with a single arm for accelerated approval -- especially in a pre-treated population where they have limited time left -- I am very concerned about

finding out about toxicity after something is on market and has hurt people."

Question 8: In the adjuvant setting, how does disease-free survival (DFS) compare to survival as an endpoint? Five-year DFS correlates with survival, and panel members believe three-year DFS will correlate, but they want further confirmation of that.

This concept made intuitive sense to some panel members. One said, "I think what most oncologists are doing today is taking high risk patients and offering combination therapy...though we don't know if that offers benefit…We need more analysis to be absolutely comfortable that this (3-year DFS) is an endpoint we want to routinely use...I wouldn't come out strongly at this point recommending it." Another commented, "I'm speaking in support of using three-year DFS. It makes sense to me and has for a long time…I think two years is too short, and five years is too long."

A Mayo Clinic statistician is working on figuring this out. He also looked at whether DFS at three years is a predictor of five-year overall survival in adjuvant colon cancer. If so, it would allow more rapid completion and reporting of CRC clinical trials. With about half the data available so far, he concluded that overall, 3-year DFS seems to predict five-year survival, but when the various arms of the studies are examined, the predictive value goes down. He said, "Graphically I would say it looks pretty good for comparison…3-year DFS=.05+.93*5 year OS. The correlation coefficient is very high…On an arm-by-arm basis, three-year DFS is an excellent predictor of five year OS. The event rates are virtually identical…(However) 3-year DFS may slightly overestimate 5-year OS and may change the conclusion in a non-trivial proportion of trials…Overall, 3-year DFS looked pretty good…but the experimental arms tended to over-estimate DFS, and the control arms tended to have DFS underestimated. So, when you look at that, the difference become something to worry about….And the relevance of 3-year-DFS for non-cytotoxic trials (biologics) is hard to say…When we get targeted therapy, it may have a mechanism of action on the tumor, but who knows what other mechanisms that may have? Whether this translates to survival in that setting is an open question…I'd say we are not ready for prime time yet with this...but it looks very promising."

The MOSAIC trial (Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer) data, which will be presented at ASCO 2004, may provide some more insight into this issue. A panel member said, "It will be very interesting...to see how the three-year data holds up at five years. One of my concerns – and I'm hopeful we will address that in the current generation of adjuvant trials -- is the confounding variables we are beginning to identify…For example, not all Stage 2 patients are alike. There is a tendency to lump them together, and the same holds true for Stage 3 patients…My concern is lumping patients together."

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