Cancer Clinical trial conundrum

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Should Oncology Drug Regulation Be Different?

- Life-threatening nature of diseases--patient access *vs* necessary data for approval
- Drugs multiple action modes; combinations
- Risk/benefit ratio--different perspective on serious adverse events; highly trained specialists using drugs rather than GP
- Product label and off-label uses

What and why of Clinical trial

- Phase I
- Phase II
- Phase III
- Phase IV
- Better treatments and hope for tomorrow
- Eliminate the less useful treatment

Risks in Developing Oncology Drugs

- Indication--lack of predictive models
- “Creative Indications”--progressively more refractory patient, market share
- Two trials versus one trial
- Dose ranging studies--moving away from MTD

Oncology Trial Concerns

Minimize bias

- Blinding trials (few)
- Endpoints that minimize bias
- Internal consistency of subgroups, endpoints

Magnitude of change of endpoint

- Clinical significance
- Underpowered trials--guessing treatment effect

Isolating effect of drug

Endpoints for traditional approval: Survival

Defined as the time from randomization to death

Unambiguous endpoint that is not subject to investigator interpretation or bias from unblinded studies

Assessed daily

Basis for NDA Approval

Demonstration of efficacy with acceptable safety in adequate and well-controlled studie**s**

Ability to generate product labeling that

- Defines an appropriate patient population
- Provides adequate information to enable safe and effective use
- Approval for an indication, not drug

Regulatory Terms

Accelerated Approval--serious or life-threatening disease, benefit over available therapy. **Use of surrogate; mandated phase IV trials**

Fast Track--life-threatening disease, potential to address unmet medical need. **Rolling NDA, meetings**

Priority review--drug would be a significant improvement compared to available drugs. **Review of NDA in 6 months**

Activity *vs.* Benefit

Biologic Activity--screening of a compound, phase II trial endpoint, an indication for further study

Clinical benefit--what is meaningful to a patient

The approval process is not a screening process for drug activity

Traditional Endpoints: Survival

Non-inferior or improved survival constitutes “patient benefit” after consideration of toxicity and the magnitude of the benefit

Non-inferior outcome ensures that a survival advantage associated with an approved drug will not be lost with a new agent

Time to Progression--Advantages

Could use a smaller sample size and shorter follow-up than trials that require a survival endpoint

Differences will not be obscured by secondary therapy if cross-over effect exists

“Time to symptomatic progression”

Response Rate

Unique endpoint--treatment is “entirely” responsible for tumor reduction

In contrast, survival and TTP have an effect of the natural history PLUS treatment effect

Must consider duration of response

Does not include stable disease

Pick your criteria and stick with it

Accelerated Approval

- Docetaxel
- Irinotecan
- Doxorubicin HCl liposome
- Capecitabine
- Cytarabine liposomal injection
- Temozolomide
- Amifostine
- Gemtuzumab
- imatinib mesylate

Challenges for Oncology Drug Regulations

- New “targeted therapies”
  - Re-define definitions of diseases
  - Greater efficacy in selected population may result in smaller patient populations
  - Novel surrogates to be validated
  - Dosing aimed at target rather than MTD
  - Dose studies, chronic administration

Challenges

- Greater number of candidate drugs
  - Careful selection of agents to demonstrate clinical benefit by oncology community
  - Patient accrual to trials need to be increased
  - Patients entering trials should reflect the patient population which will eventually use the drug
  - International studies, international agreement of endpoints and study design and approval criteria