Determining Value in Cancer Care: Role of FDA Review Process

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Demonstration of "Clinical Benefit" Required for FDA Approval

- Since 1962: evidence of effectiveness from adequate and well controlled trials
- Effectiveness = benefit to patient
- Most significant driver of evidence generation in all of medicine
- Definition has evolved over last 50 years

What is “Clinical Benefit” and how does it relate to “Value”

- Clinical benefit= something patients value: longer life, better function, better quality of life
- Practically speaking, defined by the endpoints that are accepted by FDA in efficacy trials
- Does not include concept of cost effectiveness

Endpoints in Oncology

- Survival and improvement in patient reported symptoms considered clinical benefit
- Objective Response Rate and Time to Progression usually viewed as surrogates
- Exceptions : relatively non-toxic products such as hormonal therapies or some biologics

Potential palliative endpoint: Health-related quality of life

- Pro: Patient's perspective on treatment
- Con:
  - Blinding is essential, but difficult to do
  - Careful serial assessments
    - Missing data makes interpretation problematic
    - Multiple endpoints and comparisons to baseline must be adjusted for in the statistical analysis plan
  - Clinical significance of score changes may be unclear
  - Is additional information gained, compared to a careful recording of toxicity/symptom data?

Palliation and Patient Reported Outcomes

- Blinding and associated antitumor effects (response rates) lend credibility
  - Use simple instruments
  - Hypothesis-driven
  - Avoid multiple endpoints
  - Example: Photofrin PDT and dysphagia scale

Surrogate Endpoints: "Accelerated Approval" Regulations

- For serious or life-threatening diseases
- Where the drug appears to provide benefit over available therapy
- Approval based on a surrogate that is reasonably likely to predict clinical benefit
- Put in place during AIDs epidemic; long sought by cancer community

Accelerated Approval

- Subject to the requirement that the applicant verify and describe benefit
- Post-marketing studies looking at benefit should usually be underway at the time of approval based on a surrogate
- The applicant shall carry out such studies with due diligence

Is TTP a Clinical Benefit Measure?

- Does TTP have clinical meaning?
  - Cancer growth leads to suffering and death
  - Delaying cancer growth is good
  - It some circumstances it may be something a patient can view as benefit—e.g., when treatment effect is large
  - In other cases, merely a lab or radiologic finding with questionable patient impact

Comparisons

Survival	TTP
• 100% Accurate Event	Less Accurate
• 100% Accurate Time	Less Accurate
• Assessed Daily	Assessed every 2-6 months
• Importance Unquestioned	Uncertain
• Both Safety & Efficacy	Only Efficacy
• Takes Longer	Faster
• Might be Obscured by Secondary Rx	Not Obscured

Progression-free survival

PFS would be more persuasive benefit measure when:

- When symptoms frequently occur at or soon after progression time
- When TTP increment is large
- When treatment toxicity is low
- When benefit of available drugs is less

Complicated Picture of RR as a Surrogate for Patient Benefit

- Number of CRs *vs* PRs?
- Duration of responses?
- Location of responses (e.g., liver *vs* skin)?
- Association with symptom improvement?
- Extent or bulk of metastatic disease?
- These details really matter

Cancer Drug Development: Complications in Determining Efficacy

- Fewer than 5% of cancer therapeutics entering Phase 1 reach the market
- While pharmaceutical discovery and candidate selection is highly driven by recent discoveries, most clinical oncology development is empirical, i.e., trial and error
- For example, molecularly targeted therapies developed without means to assess pharmacodynamic effect on target

Cancer Drug Development: Additional Complications

- 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

Results of Current Process

- Significant numbers of new cancer drugs coming on the market
- Many viewed as therapeutic advances
- As usual, not all questions answered at time of approval

Indications Approved during July, 2005 to December 2007

- During this period of time, 53 new indications (18 New Molecular Entities) were approved
- During this same time period, only 5 indications (5 New Molecular Entities) were not approved
- During this same time period, only two applications were withdrawn by the Sponsor

Products Approved

- Of the 53 new indications—
- 39 priority and 14 standard reviews
- 18 New Molecular Entities (NMEs), 35 supplemental applications (sNDAs or sBLAs)

Types of Approvals

- 38 Regular Approval indications (demonstration of clinical benefit)
- 10 Accelerated approval indications
- 5 previous accelerated approvals converted to regular approvals (completion of confirmatory trials with new indication)

Examples of Endpoints Used in Approved Indications

- *Overall survival*: 10 indications
- *Disease-free survival*: 5 indications
- *Progression-free survival or time-to-progression*: 12 indications
- *Response rates:* 17 indications
- *Examples of novel endpoints*: reduction in hepatic iron, depletion of asparagine

Examples of Approvals for "Rare" Diseases: Another Complication

- *Imatinib mesylate*: Dermatofibrosarcoma protuberans; Aggressive systemic mastocytosis;Hypereosinophilic syndrome/chronic eosinophilic leukemia; Relapsed/refractory pediatric PH+ ALL
- *Vorinostat*: Cutaneous T-cell lymphoma
- *Bortezomib*: Mantle cell lymphoma
- *Eculizamab*: Paroxysmal Nocturnal Hemoglobinuria

Products Not Approved

- Genasense for CLL
- Atrasentan for HRPC
- Oral beclomethasone dipropionate for GVHD
- Xcytrin for brain metastasis from NSCLC
- Mifameratide for adjuvant osteosarcoma
- Four of the above did not meet primary endpoint of pivotal registration trial

Summary: July 2005 to December, 2007

- Changes in the disease –treatment paradigm because of multiple approvals
  - *Multiple myeloma and related diseases* --doxil, thalidomide, lenolidamide, bortezomib supplements
  - *Renal cell carcinoma* --sorafenib, sunitinib, temsirolimus
  - *CML* --desatinib, nilotinib, imatinib supplements
  - *Breast cancer* -- letrozole (adjuvant), anastrozole (adjuvant), exemestane (adjuvant), raloxifene (chemoprevention), ixabepilone, lapatinib, trastuzumab (adjuvant)

Summary: July 2005 to December, 2007

- Changes in the disease –treatment paradigm because of multiple approvals
  - *Colorectal cancer* --panitumumab, cetuximab (accel approval to regular approval), bevacizumab
  - *Pancreatic*, *Gastric*, *GIST*, *hepatoma* --erlotinib (pancreas), docetaxel (gastric), sunitinib (GIST), sorafenib (hepatoma)
  - *Lung cancer* --oral topotecan (small cell), bevacizumab
  - *Head and Neck cancer* —cetuximab, docetaxel

Summary: July 2005 to December, 2007

- Changes in the disease –treatment paradigm because of multiple approvals
  - Hematologic malignancies --Myleodysplastic disease(lenalidomide, decibabine); T-cell ALL (nelarabine), lymphomas (rituximab), pegaspargase (ALL), mantle cell lymphoma (bortezomib), B cell CLL (alemtuzumab)
  - Gyne malignancies—topotecan (cervical), gemcitabine (ovarian)

Summary: July 2005 to December, 2007

- Pediatric indications/populations studied: Exjade, pegaspargase, nelarabine, imatinib supplements
- Supportive care products: Exjade (iron overload, dalteparin (DVT in cancer patients), dexrazoxane (anthracycline extravasation), cytarabine (neoplastic meningitis)

Accelerated Approval

- The importance of confirmatory trials being underway at the time of AA
- The approach of studying slightly different populations in the confirmatory setting than the AA population
- Relative merits of different trial designs
  - single arm in refractory populations
  - randomized trials in less refractory patients

Accelerated Approval

- Docetaxel (Taxotere)
- Irinotecan (Camptosar)
- Doxorubicin HCl liposome (Doxil--2 indications)
- Capecitabine (Xeloda)
- Cytarabine liposomal injection (Depocyt)
- Temozolomide (Temodar)
- Amifostine (Ethyol)--sNDA
- Celecoxib (Celebrex)
- Gemtuzumab (Mylotarg)
- Gleevec (imatinib mesylate) (STI 1571)

Endpoints Utilized

- Single arm trials : ORR
- Randomized Setting : Cytologic response, number of polyps, ORR, TTP , DFS, L VEF ; CHF

Oncology Activity--INDs

- Progressing increases in number of INDs: FY 2008 estimate IND submissions are 156% of FY 2003 IND submissions
- 2003—925 INDs; 2006—954 INDs, 2007—1115 INDs, 2008—1440 INDs

Toward a New Approach to Value in Oncology Drug Development

- Difficulty showing effectiveness is linked to problems demonstrating value
- Currently, most oncology drugs don't benefit exposed patients uniformly and treatment effect often small—decreases value for non-responders
- Safety problems also decrease value by causing injuries, personal trauma, inconvenience and raising costs
- Currently, little ability to predict which patients will be harmed

Development of Predictive Biomarkers to Improve Efficacy

- Genomic markers for tumor susceptibility
- Imaging technologies for better assessing immediate response (should not get drug for 6 months if tumor unresponsive)
- Proteomic markers for tumor subsetting
- Potential use of circulating tumor cells
- All these and other need to be rigorously assessed before adoption

Development of Predictive Biomarkers for Improved Safety

- Drug metabolizing enzymes and drug transporters: understanding impact of genetic polymorphisms
  - MTD approach to cancer drug development seriously flawed
  - May under-dose most due to sensitive outliers
  - Polymorphic enzymes: few would deliberately administer a 10X overdose, but it happens with empirical dosing
- Rare serious adverse events: finding predictive markers—this is occurring in other fields

Better Patient Reported Outcome Instruments

- If we want to know what the patient thinks, we have to ask the patient
- Problem has been adequate instruments for drug development
- Need integration into drug development
- Will be of extreme importance as cancers change to chronic rather than rapidly fatal diseases

Underlying Challenges to Demonstrating Value in Cancer Drug Development

- 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

Summary

- Drug development leading to FDA approval is an important step in evidence development for cancer drugs
- Predicated on showing of effectiveness that outweighs the harm (usually is a lot of harm)
- New methods of targeting therapy have the potential to markedly increase value by increasing the size of the treatment effect and decreasing harm
- It is worth aggressively pursuing these goals