Regulatory Perspective: Acute Leukemia Clinical Endpoints

Nancy S. Scher, MD, FACP

DODP, CDER, FDA

Outline

- Drug approval regulations
- Regular vs. accelerated approval
- Approvals for acute leukemia
- Recent lessons learned
  - Clolar (Clofaribine)
  - Zarnestra (Tipifarnib)

Requirements for Drug Approval

- Safety (FD&C Act 1938)
- Efficacy (1962 amendment)
  - Substantial evidence
  - Demonstrated in adequate and well-controlled studies
- Specific indication
- Defined patient population

Approval Pathways

- Regular approval
  - Clinical benefit (CB) or
  - Established surrogate for CB
- Accelerated approval (Subpart H, 1992)
  - Surrogate endpoint *reasonably likely* to predict CB

Regular Approval

- Clinical benefit (CB)
  - Longer life or
  - “Better” life
- Established surrogate for CB
  - e.g. Durable complete response in acute leukemia

Accelerated Approval

- Serious or life-threatening disease
- Drug provides benefit over *available therapy*
- Surrogate endpoint *reasonably likely* to predict clinical benefit
- Subsequent confirmation of clinical benefit is required (Post-approval commitment)

ENDPOINTS FOR APPROVAL DODP (1/1/90-11/1/02)

- Approvals based on endpoints other than survival
  - All approvals: 73% (48/66)
  - Regular approval: 68% (39/57)
  - Accelerated approval (AA) 100% (14/14)
- Tumor response basis for 26/57 regular approvals (plus 9/26 had relief of symptoms)
- Tumor response basis for 12/14 AA
- Symptom relief supported 13/57 regular approvals

Randomized vs. Single Arm Trials

- Single arm trials have been used in relapsed disease, with AA based on response rate
- Randomized trials (RT) permit evaluation of therapy in less refractory populations and variety of endpoints (Survival, TTP, QOL)
- Randomization may control for population heterogeneity

Patient Reported Outcomes

- Limitations to Tumor-Related Symptoms, Quality of Life, as Endpoint for approval
  - Need for validated instruments
  - Lack of blinding
  - Missing data
  - Differences must be clinically meaningful
- Health related QOL has not been used as a basis for approval in acute leukemia

Acute Leukemia Approvals

Drug	Indication	Date	Trial (s)	Benefit
Ara-C	ANLL /ALL	1969		
Daunorubicin	ANLL/ALL	1979	Single and Randomized	CR +duration
Idarubicin	ANLL (first line comb)	1990	Randomized vs Ara-Dau	CR+dur. Survival
Teniposide	Ped ALL refractory	1992	Single Arm	CR +duration

Regular Approvals for APL, MDS

Drug	Indication	Date	Trial (s)	Benefit
ATRA (Vesanoid)	Second line APL	1995	Single arm 2 cohorts	CR 73-80%
Arsenic trioxide (Trisenox)	Second line APL	2000	Single arm	CR 70% Cytogen.&Dur.
Azacytidine (Vidaza)	MDS	2004	Randomized 2 single arm	RR 16% Improved 19% *[AML 1/10 CR, 1/10 PR]*

Accelerated Approvals for Acute Leukemia

Drug	Indication	Date	Trial (s)	Benefit
Mylotarg (Gemtuzumab ozogamicin)	Age>60, CD33+, 2nd line; can't take chemo	2000	3 single arm	CR + CRp (16%+13%) = 30% overall
Clolar (Clofaribine)	Relapsed/ refractory ped ALL	2004	Single arm	CR + CRp 12.2% (6/49) 8.2% (4/49)

Mylotarg (gemtuzumab ozogamicin)

- 3 single arm trials (n=142)
- Adults CD33 + AML in first relapse
- Overall 3 trials: CR+CRp (16+13%) = 30%
- Age ≥60 (n=80): CR+CRp (15+11%)=26%
- CRp=Platelet recovery <100,000/μL
- AA: Age ≥ 60 + aggressive Rx unsuitable
- Post-marketing safety concerns

Clolar (clofaribine)

- Relapsed/refractory pediatric ALL
- Approved on CR+CRp in single arm trial
- Early transplant
  - Responses often not confirmed (no 2nd BM)
  - Duration of CR not confirmed
- CR+CRp: Surrogate *reasonably likely* to predict CB
- Can “bridge to transplant” be a surrogate?

Zarnestra (tipifarnib)

- Proposed: Treatment of elderly patients with newly diagnosed poor-risk AML
- Single arm trial(s)
- Age ≥ 75 or age 65-74 with prior MDS
- CR 11% (15/135)
- MDR 275 days (95% CI 127-376)
- Mortality 1-month 12%; Rx-related deaths 7%
- ODAC 5/05: Heterogenous population

Summary

- Regular approval
  - Clinical benefit (CB)
  - Effect on Established surrogate for CB [CR+Duration]
- Accelerated Approval
  - Effect on Surrogate *reasonably likely* to predict CB [CR+CRp]
- Challenges
  - Trial design
  - Endpoints

Summary$_2$

- Challenges
  - Trial design
    - Single arm trial limitations
    - Population not defined/heterogeneous
    - Confounding effect of transplant
  - ENDPOINTS

Summary$_3$

- Challenges: ENDPOINTS
  - Traditional
    - Magnitude and duration of CR
    - Quality of CR (e.g. CRi, CRp)
  - Patient Reported Outcomes (QOL)
  - Advances in Biology and Molecular Genetics
    - Molecular CR (MRD)
    - Cytogenetic CR