ASH/FDA Workshop on Clinical Endpoints in Multiple Myeloma

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Bortezomib: From Bench to Bedside

1994 NF-κB is a therapeutic target in myeloma

1995-7 Drug discovered (Julian Adams), NCI 60 cell line

1998 Phase I trials started

2000 Phase I trials:safe and has anti-MM activity

2000 Targets MM cell and BM microenvironment to overcome drug resistance in laboratory and animal studies

2001 Phase II trial: 35% responses(including CRs), duration 12 months, with associated clinical benefit shows remarkable responses in patients with advanced disease unresponsive to known therapies

Bortezomib: From Bench to Bedside

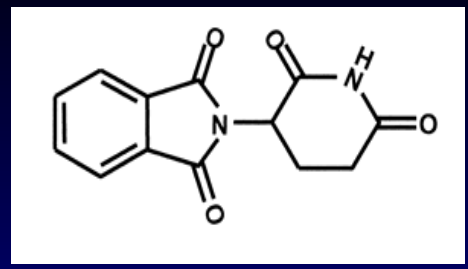
2003 Accelerated approval for relapsed refractory disease by FDA

2003 Phase III trial fully accrued and stopped early due to delay in TTP in Bortezomib cohort. Response rate, 1 year and OS all significantly greater with Bortezomib

2005 FDA approval extended to relapsed myeloma

2005 High overall and extent of response with Dex and MP for transplant and non transplant recipients, respectively.

Thalidomide in Myeloma



- ≥ 50 decreased paraprotein in 30% relapsed and/or refractory MM
- 47% response when combined with dexamethasone (Dex) in Dex refractory MM
- 63% response when combined with Dex versus 41% to Dex as initial therapy (FDA approved May 2006)
- Does not compromise subsequent PBSC mobilization and collection
- MPT increases overall and extent of response, as well as prolongs PFS and OS compared to MP and MEL 100 x2 as initial therapy of elderly patients

Barlogie et al. Blood 98: 492, 2001
Anagnostopoulos et al. Brit J Hematol 121:768, 2003.
Rajkumar et al. J Clin Oncol 2005, in press.
Palumbo et al. Blood 104(Suppl): 63a, 2004.

Bench to Bedside Development Of Lenalidomide

- Preclinical (2000): targets tumor (caspase-8 mediated apoptosis) and microenvironment in vitro and in vivo in animal model
- Phase I trial (25 patients, 2001): MTD 25 mg; favorable toxicity; stable disease or response in 79% patients
- Phase II trials (324 patients, 2002-3): confirmed responses and decreased neuropathy, constipation, and somnolence compared to thalidomide; Dex improved responses
- Two Phase III trials (700 patients, 2003-4): Lenalidomide/Dex versus Dex/placebo in relapsed myeloma: FDA approved June 2006 for relapsed myeloma (OR,CR,TTP,OS)
- Phase II trial (34 patients, 2005) 91% responses, with 6% CR and 32% nCR as initial therapy for transplant candidates; MPR promising for non-transplant candidates.

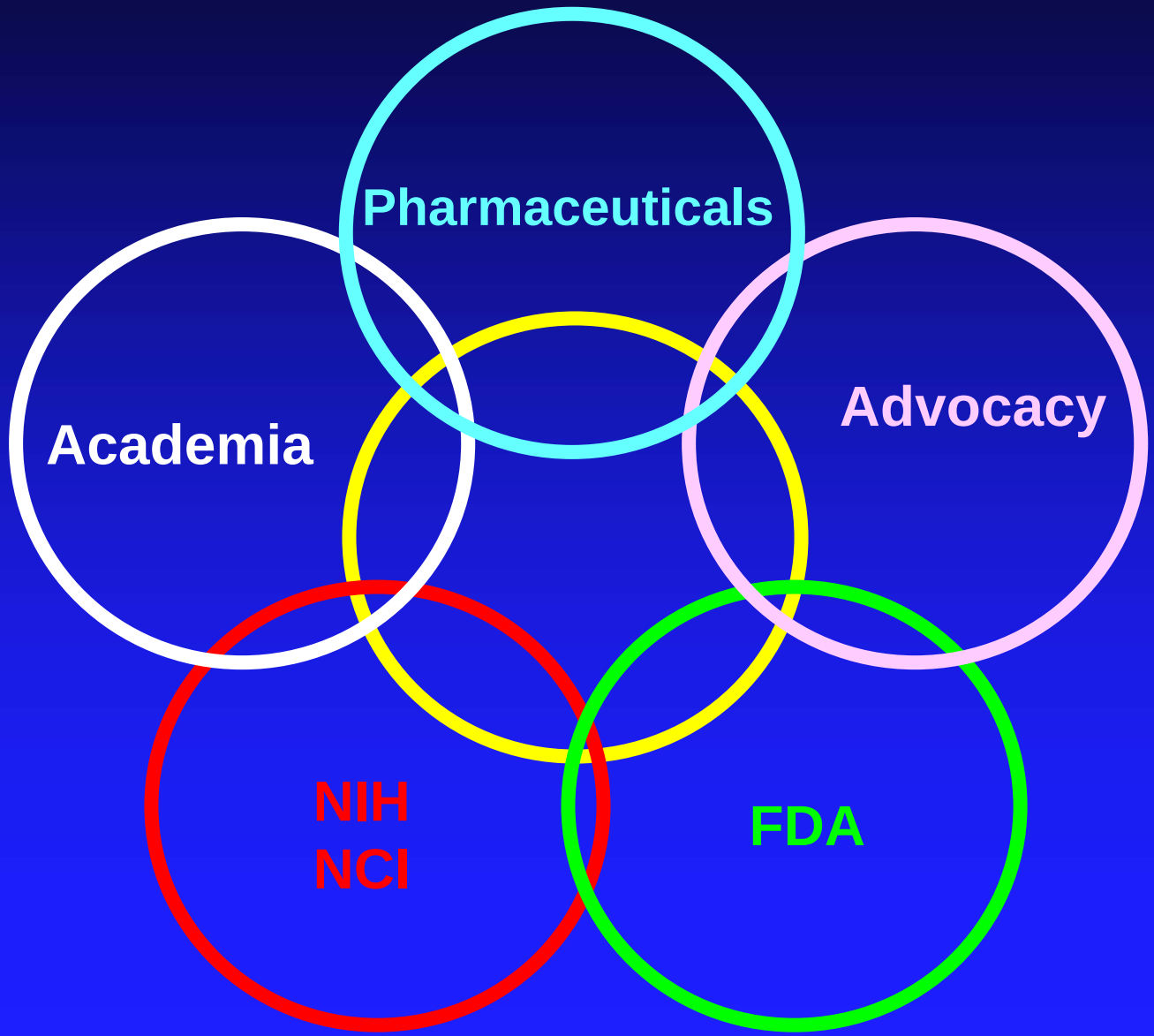
Integration of Novel Therapy Into Myeloma Management

>> Treatment of Relapsed/Refractory MM (single agent/combinations)

>> Induction/First-line Therapy

>> Transplant/Maintenance

Opportunities for Rapid Translation of Advances from Bench to Bedside



Bortezomib as Example

1. Rapid bench to bedside and approval.
2. FDA, NCI, academia, pharmaceuticals, advocacy (MMRF).
3. NCI 60 cell line panel – drug related proteasome inhibition correlated with growth inhibition.
4. Overcame conventional drug resistance using in vitro and in vivo preclinical models.
5. In vivo pharmacology defined dose/schedule for Phase I.

Anderson, Pazdur, Farrell. J Clin Oncol 2005; 23: 7207-11

Bortezomib as Example (cont)

- 6. NDA – 2 Phase II trials (54, 202 pts).
- 7. EBMT response criteria.
- 8. Independent review committee.
- 9. Responses, including durable CRs, clinical benefit led to accelerated approval in relapsed refractory myeloma.
- 10. Phase III for full approval rapidly accrued, and extended approval to relapsed myeloma.

Anderson, Pazdur, Farrell. J Clin Oncol 2005; 23: 7207-11

Lessons of Bortezomib

1. Biological target to guide clinical and preclinical development.

2. Early partnership with FDA, NCI, academic investigators, pharmaceuticals, advocacy.

3. Rapid accrual to clinical trials with durable CR as endpoint for accelerated approval.

Anderson, Pazdur, Farrell. J Clin Oncol 2005; 23: 7207-11

Recommendations

- 1. Preclinical safety studies should duplicate the intended schedule, duration, formulation and route of administration to be used in clinical trials.
- 2. For novel targeted therapies, the drug target should be identified and a valid biomarker assay should be developed and used to conduct PK and PD studies to define dose levels and dose escalation schemes.
- 3. The EBMT criteria to assess response have been accepted for regulatory approval of drugs for the treatment of multiple myeloma.

Anderson, Pazdur, Farrell. J Clin Oncol 2005; 23: 7207-11

Recommendations (cont)

- 4. Response rate and duration are acceptable criteria for new drug approval in patients with refractory myeloma. Based on the clinical results obtained with bortezomib, an overall response rate $\geq$ 28 percent, with a complete response rate $\geq$ 3 percent and a median response duration of 12 months have been accepted by FDA as criteria for accelerated approval.

Anderson, Pazdur, Farrell. J Clin Oncol 2005; 23: 7207-11

Recommendations (cont)

- 5. Partnerships between pharmaceutical sponsors, governmental agencies, academic investigators, clinical investigators, and patient advocacy groups should be established. With the increasing importance of combination therapy collaboration between pharmaceutical sponsors is necessary to facilitate drug development.

Anderson, Pazdur, Farrell. J Clin Oncol 2005; 23: 7207-11

Recommendations (cont)

- 6. Correlative biological studies are recommended to understand mechanisms of drug action, to determine the validity of the putative drug target, and to identify previously unsuspected drug targets.

Anderson, Pazdur, Farrell. J Clin Oncol 2005; 23: 7207-11

Second MMRF FDA Roundtable(June 2005): Strategic Framework for Novel Drug Development in Multiple Myeloma

1. FDA oncology head and FDA myeloma review teams; myeloma experts; companies with promising novel myeloma therapies; MMRF

2. For phase 1, 2, and 3 trials, defined:
   a. patient populations: unmet need,targeted
   b. design: rapid dose escalation, test combination therapy
   c. efficacy endpoints: Response by EBMT, time to progression as surrogate for survival
   d. safety endpoints: standardized

Criteria for Diagnosis of Myeloma

MGUS

- <3 g M spike
  <10% PC

AND

No anemia, bone lesions
normal calcium and
kidney function

Smoldering MM

- ≥3 g M spike
- **OR** 10% PC

Active MM

- ≥10% PC
- M spike +

AND

Anemia, bone lesions,
high calcium or
abnormal kidney function

International Myeloma Working Group. BJH 2003; 121: 749-57.

Durie-Salmon Myeloma Staging System

Criteria

Stage I

All of the following:

- Hemoglobin value > 10 g/l
- Serum calcium value normal (< 12 mg/dl)
- On roentogenogram, normal bone structure (scale)
  - or solitary bone plasmacytoma only
- Low M-component production rates
  - IgG value < 5 g/dl
  - IgA value < 3 g/dl
  - Urine light chain M-component on electrophoresis
    - < 4g/24h

Stage III

One or more of following:

- Hemoglobin value < 8.5 g/l
- Serum calcium value > 12 g/dl
- Advanced lytic bone lesions (scale 3)
- High-M-component production rates
  - IgG value > 7 g/dl
  - IgA value > > 5 g/dl
  - Urine light chain M-component on electrophoresis
    - > 12 g/24h

Durie BGM. Cancer 1975;36:842

Myeloma Prognostic Factors

Plasmablastic morphology
Serum β2 microglobulin
Labeling index
Interleukin-6
C-reactive protein
Karyotype-chromosome 13 deletion
Cell surface phenotype
Serum cytokine/receptor level
Peripheral blood plasma cells
Combinations: ↑↑ β2 microglobulin, LI (6 mo) vs
↓↓ β2 microglobulin, LI (54 mo)

Greip P. Blood 1985;65:305
Durie B. Blood 1990;75:823
Batailtie R. Blood 1992;80:733
Wizig T. Blood 1996;88:1780
Kuehl M. Nat Rev Cancer 2002;2:175

International Staging System (ISS) for Myeloma

Stage	Criteria	Median Survival (mo)
I	β 2m < 3.5 mg/L albumin $\geq$ 3.5 g/dL	62
II*	Not stage I or III	44
III	β 2m > 5.5 mg/L	29

* β 2m < 3.5 mg/L and albumin < 3.5 g/dL or
β 2m 3.5 - < 5.5 mg/dL, any albumin

Greipp et al. J Clin Oncol 2005; 23: 3412-20

International Myeloma Working Group Uniform Response Criteria: CR and Response Categories

Response	Criteria
sCR	normal FLC ratio; no clonal BM plasma cells
CR	IFX-, < 5% BM plasma cells
VGPR	IFX+ SPEP-; ≥ 50% serum and ≥ 90% urine protein decrease; ≥ 50% decrease in FLC/plasma cells
SD	not CR, VGPR, PR, or PD

Durie BGM et al. Leukemia 2006; 20: 1467-73.

Steps to Moving Novel Drug From Bench to Bedside

1. Identify target in tumor and microenvironment
2. Validate anti-tumor activity of new drug in laboratory and animal models
3. Clinical trials

Phase I	safety, dose
Phase II	efficacy
Phase III	comparison with best available therapy

ASH/FDA Workshop on Clinical Endpoints in Multiple Myeloma

Timeline

June, 2005	ASH/FDA Workshop on Endpoints in Acute Leukemia
Winter, 2006	ASH joins in co-sponsorship agreement with FDA, AACR, and ASCO outlining the clinical endpoints workshop project—taking the lead on meetings related to hematologic malignancies
Spring, 2006	Steering Committee Selected

ASH/FDA Workshop on Clinical Endpoints in Multiple Myeloma Timeline (continued)

Summer, 2006	Subcommittee Calls
September/October 2006	Steering Conference Calls

ASH/FDA Workshop on Clinical Endpoints in Multiple Myeloma

- Monoclonal Gammopathy of Unclear Significance (MGUS)
  Subcommittee Chair: Robert A. Kyle, MD
- Newly Diagnosed
  Subcommittee Chair: S. Vincent Rajkumar, MD
- Maintenance
  Subcommittee Chairs: Jean-Luc Harousseau, MD, and Keith Stewart, MD
- Relapsed
  Subcommittee Chair: Donna Weber, MD
- Refractory
  Subcommittee Chair: Paul G. Richardson, MD

Questions

Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering (Asymptomatic) Multiple Myeloma (SMM)

1. How often should the physician monitor a patient with monoclonal gammopathy of undetermined significance (MGUS)?

2. Should patients with MGUS who have a high risk of progression be treated?

3. Should patients with smoldering multiple myeloma (SMM) have both a serum M-spike $\geq$ 3 g/dL and a bone marrow containing 10% or more plasma cells?

4. Should patients with SMM be treated?

5. Does the reduction of bone marrow plasma cells and/or decrease in the serum M-spike from therapy prolong the time to progression to a malignant plasma cell proliferative process?

6. Why is the frequency of MGUS increased in African Americans?

Questions

Newly Diagnosed

1. Are there any concerns about having CR as a regulatory endpoint for newly diagnosed myeloma?

2. Is there agreement that CR is the goal of current therapy for myeloma, and all efforts should be made to achieve CR?

3. What are the consequences of not having CR as a regulatory endpoint in newly diagnosed myeloma? What are the benefits?

4. Would equivalence in CR rates be adequate?

5. Is there agreement that overall response rate is inadequate?

6. Can patient reported measures using the ECOG QOL tool if validated be used for regulatory purposes?

Questions

Maintenance

1. Is the proposed definition of maintenance therapy acceptable?

2. Is restriction of term "maintenance" to newly diagnosed induction therapies acceptable?

3. Is CR an acceptable endpoint for maintenance therapies?

4. Is the triad of improved CR, EFS and quality of life a useful endpoint?

5. Can patient reported QOL be used for regulatory purposes?

Questions

Relapsed

1. What is an acceptable definition of early relapse?

2. Are response criteria reasonable endpoints for full or accelerated approval of new agents in patients with early relapse of multiple myeloma?

3. Are benefits in response and survival that are only noted in subgroups of patients with poor risk myeloma (particularly based on cytogenetics) reasonable endpoints to justify full or accelerated approval for new agents?

4. Are there special circumstances where other endpoints would be reasonable to assess a new agent (ie, time to skeletal related event)?

5. If response criteria are acceptable endpoints, should free light chain criteria be included as acceptable measures?

6. Is there any role for additional endpoints such as time to retreatment or quality of life measures (and how should these be measured)?

Questions

Refractory

1. Definition of relapsed and refractory

2. Definition of a non-responding but non- progressive subset – "plateau phase“ type pts

3. Consideration of adequate therapy to define treatment failure per 1)

4. Definition of treatment intolerant vs truly refractory and drug resistant – practical considerations suggest this amounts to the same, but in specific settings how should this be considered?

5. Traditional endpoints to be confirmed - RR (incl CR); DOR; PFS; OS – key points Blade criteria vs IMW new classification- new criteria require validation: Blade remains gold standard until this is done; preference for PFS vs TTP, or EFS

6. Role of biomarkers? eg PET, Cytogenetics - validation required