Development of Effective New Treatments for Multiple Myeloma

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INTRODUCTION

Despite recent advances in basic biology and treatment, multiple myeloma remains incurable, and the need to develop effective new treatments remains urgent. The focused development of effective treatments for myeloma requires cooperation between patients, the US Food and Drug Administration, pharmaceutical sponsors, researchers working in both government and academia, and practicing oncologists. With approximately 50,000 people alive with myeloma annually in the United States, multiple myeloma represents a relatively small market compared with other oncology indications and areas such as cardiovascular disease. For this reason, pharmaceutical developers may be less apt to take on the full burden and risk of developing new drugs for this disease.

Despite this limitation, multiple myeloma represents a unique and attractive opportunity for expedited new drug development for five reasons. First, there is a clear unmet medical need in myeloma. Second, the clinical end points for rapid new drug approval in myeloma have been clearly identified and can be measured using commercially available laboratory and radiologic tests.

Third, the US Food and Drug Administration has identified response rate with substantial duration as a valid end point for regulatory approval of new myeloma agents under accelerated approval (AA; subpart H).

Under these provisions, drugs used in serious and life-threatening diseases may be approved if they demonstrate an improvement over available therapy on the basis of a surrogate end point “reasonably likely to predict clinical benefit.” Subsequent randomized trials demonstrating clinical benefit are required after AA. The clinical profile of bortezomib (recently approved for the treatment of patients with relapsed and refractory myeloma), including an overall response rate ≥ 28%, with a complete response rate ≥ 3% and a median response duration of 12 months in patients refractory to all available treatments, has been accepted by US Food and Drug Administration as surrogate evidence deemed reasonably likely to predict clinical benefit and, therefore, as meeting criteria for AA.

Fourth, for the approval of bortezomib, the US Food and Drug Administration accepted the criteria of the European Group for Blood and Marrow Transplant (EBMT), as set forth by Bladé et al, for the definition of response in patients with myeloma. The EBMT criteria are now widely accepted as the standard criteria for the definition of complete and partial remission.

Fifth, the determination of response according to the EBMT criteria depends on the measurement of the levels of myeloma protein (M-protein) in serum and urine. This assay is available in commercial laboratories and can be performed reproducibly using widely available laboratory techniques. Additional components of the EBMT criteria include the percentage of plasma cells in the bone marrow and the absence of evidence of new skeletal disease by conventional x-ray. These aspects of the EBMT criteria can also be measured easily and reproducibly.

To address current challenges related to new myeloma drug development, a roundtable symposium, including members of
the US Food and Drug Administration, academia, the National Cancer Institute (NCI), the pharmaceutical industry, and the Multiple Myeloma Research Foundation (MMRF), was held in Washington, DC, on February 25, 2004. The objectives of the roundtable were to define approaches to the development of new agents and to identify strategies that can facilitate the delivery of needed therapies to myeloma patients. The members first reviewed the lessons learned from the recent approval of bortezomib, a novel antmyeloma agent. Next, preclinical development issues were addressed. Finally, questions relating to clinical trial design were considered. The findings of the roundtable, which was sponsored by the MMRF, are summarized in this report.

**THE EXAMPLE OF BORTEZOMIB**

The approval of bortezomib in 2003 marked a major advance in the treatment of patients with multiple myeloma. From the time that nuclear factor-kappa B was identified and confirmed as the bortezomib target in preclinical models to the time bortezomib received AA, the development process moved unusually rapidly, requiring only 4 to 5 years compared with the more typical time frame of 7 to 10 years. From the initial identification of bortezomib’s unique activity in the NCI 60-cell line screen, a focused development effort involving coordination among the US Food and Drug Administration, NCI, academic researchers, advocacy groups including the MMRF, clinical investigators worldwide, and the pharmaceutical sponsor was pursued.

Bortezomib’s unique mechanism of action was identified in the NCI screening program. Early studies in the NCI 60-cell line screen showed that bortezomib was potent and seemed to act by a novel mechanism; related studies showed that bortezomib’s growth-inhibitory effects correlated strongly with proteasome inhibition. Proteasome inhibition was subsequently demonstrated to inhibit nuclear factor-kappa B. The initial step in bortezomib’s development was identification and confirmation of the biologic target.

The proteasome inhibition assay served as a pharmacodynamic marker. In vivo pharmacology models were used to define dose levels and intervals for the toxicology and phase I clinical studies. Bortezomib overcame conventional drug resistance in both in vitro and in vivo models of human myeloma in the bone marrow microenvironment.

After filing of the investigational new drug application, the pharmaceutical sponsor entered into an extensive clinical trial partnership with NCI’s Cancer Therapy and Evaluation Program. Phase I trials demonstrated both an acceptable safety profile and early evidence of clinical anti-myeloma activity.

The New Drug Application (NDA) submission leading to AA of bortezomib included one dose-ranging phase II study in relapsed myeloma patients (54 patients) and one single-arm phase II study in multiply relapse myeloma patients (202 patients). Pre-NDA meetings between the pharmaceutical sponsor and US Food and Drug Administration allowed discussion of clinical trial design and clarification of clinical trial end points. The phase II study leading to new drug AA was a multicenter trial and accrued rapidly. Efficacy was determined using the EBMT criteria. An independent review committee verified responses. The responses seen in heavily pretreated patients included complete responses. The overall median response duration was 12 months. These results led the US Food and Drug Administration to approve bortezomib under AA guidelines. The sponsor ensured that the comparative phase III trial required for full approval was ongoing and rapidly accruing patients at the time of the NDA submission. The development of bortezomib highlighted the importance of identifying and using a biologic target to guide preclinical and early clinical development, of establishing early partnerships with US Food and Drug Administration, NCI, and academic investigators, and of rapid entry into clinical trials with durable complete remission as an agreed end point for AA.

**PRECLINICAL DEVELOPMENT**

Cell lines and animal models have been relatively unsuccessful in predicting the clinical efficacy of anticancer agents. Current research focuses on the development of carefully validated tumor cell line banks with known genetic profiles and well-characterized primary human tissue banks as valuable tools to improve the predictive value of preclinical testing. An area of critical focus for multiple myeloma is the development of models that more closely predict the biology of myeloma cells in the bone marrow microenvironment.

Basic pharmacology studies establish the potency and specificity of a new agent and may elucidate the mechanism of action. These studies may be incorporated in the agent’s product label at the time of approval. No specific US Food and Drug Administration requirements exist for demonstration of efficacy or proof of principle at the investigational new drug stage. The primary regulatory purposes of preclinical toxicology studies are to identify a clinical starting dose and potential organ toxicities and their reversibility and to guide dosing regimens and escalation schemes.

Pharmacokinetic and pharmacodynamic studies are critical to the delineation of dose levels, dose schedules, and escalation schemes. A valid biomarker assay may facilitate this process.

Toxicology studies should simulate the intended schedule, duration, formulation, and administration route to be used in clinical trials and should conform to the good laboratory practices as described in the US Code of Federal Regulations. The initial toxic dose is generally identified
in a rodent species and used to determine a starting dose. Nonrodent studies are used to confirm that the starting dose is appropriate. If early preclinical studies suggest specific organ toxicities, further detailed evaluation should be undertaken in the long-term toxicity studies as the drug’s clinical development progresses. Although not required by the US Food and Drug Administration for documentation of drug efficacy and safety, correlative biologic studies may provide a greater understanding of the mechanisms of drug action. These studies may determine whether the drug target is being inhibited in responding patients, identify previously unrecognized drug targets, and assist in designing combination treatment regimens.

**CLINICAL TRIALS**

The US Food and Drug Administration and the pharmaceutical sponsor must initially agree on clearly defined clinical study end points. The US Food and Drug Administration has identified a substantial response rate with a clinically meaningful duration as end points for AA in multiple myeloma. The response determination can be made using the widely available and reproducible measurement of M-protein levels in serum and/or urine according to the EBMT accepted criteria. Complete response by EBMT criteria requires demonstration of complete disappearance of serum and urine M-protein, the presence of less than 5% plasma cells in the bone marrow aspirate or biopsy, and no increase in skeletal lesions by x-ray examination.

Approval requires that sponsors must demonstrate that agents are safe and must provide substantial evidence of effectiveness from “adequate and well-controlled investigations.” The clinical trial design for regulatory submission is influenced by the type of regulatory approval sought (regular or accelerated). Regular approval requires the demonstration of clinical benefit, which is usually defined as an improvement in survival, disease-related symptoms, or an established surrogate. In 1992, new regulations allowed for AA of drugs that were intended for serious or life-threatening diseases and showed an improvement over available therapy.

AAs are based on an effect on an end point other than mortality or irreversible morbidity. These approvals usually use surrogate end points that are “reasonably likely to predict clinical benefit.” In multiple myeloma, the US Food and Drug Administration has used a clinical response rate with sufficient duration as a surrogate to be reasonably likely to predict clinical benefit in relapsed and refractory patients. On the basis of the clinical results obtained with bortezomib, which was recently approved for the treatment of patients with relapsed and refractory myeloma, the US Food and Drug Administration has accepted an overall response rate $\geq 28\%$, with a complete response rate $\geq 3\%$ and a median response duration of 12 months in patients refractory to all available treatments, as evidence satisfying the AA regulatory considerations. AA regulations stipulate that a drug approved under AA is subject to the condition that the sponsor conduct studies to verify and describe the actual clinical benefit. At the time of approval, a randomized phase III trial comparing single-agent bortezomib with single-agent high-dose dexamethasone in patients with multiple myeloma who had relapsed after one to three prior therapies was well underway with considerable accrual. The primary end point of the trial was time to progression, with a secondary end point of overall survival. The ongoing study with sufficient patient enrollment at the time of AA ensured that the approval under AA regulations would not interfere with completion of the trial designed to provide confirmation of clinical benefit.

A novel agent’s efficacy is most reliably demonstrated by statistically significant improvement in a clinically meaningful end point in blinded, randomized, controlled trials. The agent’s effectiveness must be clearly distinguished and not confounded by the natural history of the disease. In settings where there is available therapy, comparison trials are performed that will isolate the effect of the agent.

Add-on trials and direct comparison trials of single agents can be designed to demonstrate either superiority or noninferiority to an available therapy. The add-on design (ie, A+B v B v A) usually combines a novel agent (A) with an available therapy (B). The trial compares this new combination with available therapy and with the new agent administered alone. This type of randomized trial allows isolation of the effect of the novel agent by examining differences in response rate, time to progression, or survival of the add-on combination compared with available therapy.

Single-arm studies may be performed for drug registration. Settings for single-arm studies may include those where no available therapy exists and where major tumor regressions occur infrequently in the absence of treatment. The bortezomib studies enrolled multiply relapsed myeloma patients. Patients entered onto the major phase II study had a median of six prior regimens. In these single-arm studies, response rate and response duration have been accepted as substantial evidence supporting AA in settings where no effective available therapy exists. The disease and patient population studied in bortezomib’s single-arm studies met these criteria.

Response criteria used by regulatory agencies must accurately assess the therapeutic intervention and have wide acceptance by the clinical trial community. Thus, the EBMT criteria were used in bortezomib’s regulatory submission.

Frequently, response rates (especially complete response rates) are small in true refractory disease settings. Hence, testing novel agents in heavily pretreated patients may result in effective therapies being discarded because of failure to demonstrate efficacy. The US Food and Drug Administration recognizes that novel therapies can also be tested in newly diagnosed patients. The novel agent can be used in a window treatment study where newly diagnosed patients
patients receive a novel drug for a short period to document antitumor activity before the initiation of standard therapy. The window period allows assessment of activity without compromising patients’ access to established therapy of potential greater efficacy at the earliest sign of disease progression.

**RECOMMENDATIONS**

Multiple myeloma offers an opportunity for clinical investigators and commercial sponsors to expedite the development of novel agents. A greater understanding of molecular targets and the complex pathogenesis of multiple myeloma has enabled the development of an array of new therapeutic agents for this disease with limited therapeutic options. Clearly defined and easily measurable clinical end points of response rates with significant duration have been identified by the US Food and Drug Administration as end points for AA of new myeloma agents. This clarity, along with continuing advice from the US Food and Drug Administration during the development process, will expedite the new agent’s commercial availability.

The following are the specific recommendations that resulted from the roundtable symposium held in Washington, DC, on February 25, 2004. First, preclinical safety studies should duplicate the intended schedule, duration, formulation, and route of administration to be used in clinical trials. Second, for novel targeted therapies, the drug target should be identified and a valid biomarker assay should be developed and used to conduct pharmacokinetic and pharmacodynamic studies to define dose levels and dose-escalation schemes. Third, the EBMT criteria to assess response have been accepted for regulatory approval of drugs for the treatment of multiple myeloma. Fourth, response rate and duration are acceptable criteria for new drug approval in patients with refractory myeloma. On the basis of the clinical results obtained with bortezomib, an overall response rate ≥ 28%, a complete response rate ≥ 3%, and a median response duration of 12 months have been accepted by US Food and Drug Administration as criteria for AA. Fifth, partnerships between pharmaceutical sponsors, government 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. Finally, correlative biologic 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. A schematic representation of new myeloma drug development is shown in Figure 1.

**Appendix**

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Authors’ Disclosures of Potential Conflicts of Interest

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