Brief report

Seven-year median time to progression with thalidomide for smoldering myeloma: partial response identifies subset requiring earlier salvage therapy for symptomatic disease

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Smoldering multiple myeloma (SMM) is usually followed expectantly without therapy. We conducted a phase 2 trial in 76 eligible patients with SMM, combining thalidomide (THAL, 200 mg/d) with monthly pamidronate. In the first 2 years, THAL dose reduction was required in 86% and drug was discontinued in 50%. Within 4 years, 63% improved, including 25% qualifying for partial response (PR); by then, 34 patients had progressed and 17 required salvage therapy. Unexpectedly, attaining PR status was associated with a shorter time to salvage therapy for disease progression ($P < .001$), perhaps reflecting greater drug sensitivity of more aggressive disease. Low beta-2-microglobulin levels less than 2 mg/L were independently associated with superior overall and event-free survival. Four-year survival and event-free survival estimates of 91% and 60%, respectively, together with a median postsalvage therapy survival of more than 5 years justify the conduct of a prospective randomized clinical trial to determine the clinical value of preemptive therapy in SMM. Trial registered at http://www.clinicaltrials.gov under identifier NCT00083382. (Blood. 2008;112:3122-3125

Introduction

Multiple myeloma (MM) is thought to progress, in the majority of cases, from a clinically benign precursor condition, monoclonal gammapathy of undetermined significance (MGUS).1 A more advanced form of MGUS is referred to as smoldering MM (SMM),2,3 which is characterized by a greater tumor burden but, like MGUS, by the absence in general of cytogenetic abnormalities (CAs) and magnetic resonance imaging (MRI)– or metastatic bone survey (MBS)–defined focal lesions.4 The clinical course of patients afflicted with SMM varies considerably, with a median time to progression to symptomatic disease reportedly of 1 to 2 years.5 According to a recent comprehensive review of the Mayo Clinic (Rochester, MN) records covering a 26-year interval from 1970 to 1995, 276 (8%) among 3549 patients with MM fulfilled the criteria of SMM;59% of the 276 patients developed either symptomatic MM or primary amyloidosis. Based on the proportion of bone marrow plasma cells and serum monoclonal protein levels, 3 groups with vastly differing 10-year SMM progression estimates were identified (77% vs 64% vs 33%). The recent availability of the serum-free light chain assay also aided in the prognostication of subjects with SMM, in that the free light chain ratio helped distinguish 3 risk groups with 5-year progression rates of 76%, 51%, and 25%.7

An angiogenic switch has been postulated as a pivotal event in the progression from MGUS to MM.8 In fact, our first trial with thalidomide (THAL) for advanced and refractory MM9 could be effectively exploited as a means of overcoming tumor cell resistance to traditional cytotoxic agents.11 As in the Mayo Clinic phase 2 trial reported by Rajkumar et al,12 both antiangiogenic and immunomodulatory properties of THAL13 provided a strong rationale for our group in 1998 to evaluate this noncytotoxic compound in a preemptive clinical trial aimed at delaying or even preventing the progression from SMM to overt disease. We added pamidronate (PAM), which, in addition to reducing the frequency of skeletal events in overt MM,14,15 could shrink established tumors in a severe combined immunodeficient mouse–human (SCID-hu) model system16 and induce clinical responses in patients with SMM.17 Here we report on the response rates and clinical outcomes of 76 eligible patients with SMM enrolled into protocol UARK 98-036 at the Myeloma Institute for Research and Therapy of the University of Arkansas for Medical Sciences.

Methods

The protocol was designed to enroll previously untreated patients with SMM. Diagnostic criteria included bone marrow plasmacytosis (BMPC) more than 10% and measurable disease defined as serum M-protein levels of 2 g/dL or more or urine M-protein excretion of 400 mg/d or more; osteolytic bone lesions had to be absent.3 A median time of 6 months (range, 0 to 80 months) had elapsed from initial diagnosis of SMM to protocol therapy. The treatment plan called for daily administration of THAL at a dose of 200 mg, allowing for dose reductions to as low as 50 mg applied on alternating days in the event of severe toxicities. PAM was administered monthly at a dose of 90 mg intravenously. Response criteria of the European Bone Marrow Transplant group and those set forth by a recent international panel were used.18,19 Improvement

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(IMP) required M-protein reduction by at least 25% and partial response (PR) by 50%; near-complete remission (n-CR) required absence of M-band on standard electrophoresis and complete remission (CR), absence of M-protein band on immunofixation analysis.

Kaplan-Meier methods were used to generate survival distribution graphs, and comparisons were made via the log-rank test. Running-log-rank tests were used to determine optimal cutoff values for baseline laboratory values in the multivariate analyses, which applied stepwise selection and Cox proportional hazard regression modeling. The institutional review board of the University of Arkansas for Medical Sciences approved the studies. Informed consent was obtained in accordance with the Declaration of Helsinki.

**Results and discussion**

The 76 eligible subjects collectively had features of low-stage disease by International Staging System (ISS; stage I; 90%), beta-2-microglobulin (B2M > 3.5 mg/L; 92%), and BMPC (< 20%; 62%). None had hypercalcemia more than 2.625 mM (10.5 mg/dL) or bone lesions, 1 patient had renal insufficiency (creatinine 176.8 µM [> 2 mg/dL]), and 6 others had anemia (hemoglobin < 105 g/L [10.5 g/dL] or 20 g/L [2 g/dL] less than normal); only 5% had CAs. Applying prognostic groups defined by Kyle et al, 18% qualified for group 1 (BMPC < 10%, serum M-protein < 3 g/dL) and 82%, for group 2 designation (BMPC ≥ 10%, M-protein < 3 g/dL); none was in group 3 (BMPC < 10%, M-protein ≥ 3 g/dL). With a median follow-up of 6 years, 34 have experienced disease progression, 17 of whom required salvage therapy after a median of 25 months (Figure 1A). Disease progression and need for salvage therapy were not affected by Kyle et al’s prognostic groups. The median postsalvage therapy survival is 66 months. Seventy-six percent of patients remain alive; 8 patients died after salvage therapy for progressive MM and 10 died of unrelated causes.

Two years after entry on study, THAL had been discontinued in 50% and its dosing reduced in another 36%, due in part to peripheral neuropathy (grade 3, 8%; grade 2, 18%; grade 1, 12%). Other grade 2 or higher toxicities included neutropenia and dizziness in 8%; fatigue, thrombocytopenia and cardiovascular events were each reported in 7%. PAM was discontinued in

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**Figure 1.** Kaplan-Meier plots of clinical outcomes in patients with smoldering myeloma receiving preemptive thalidomide therapy. (A) Cumulative incidence of patients experiencing disease progression and of patients receiving salvage therapy. Patients who experienced disease progression at any time after enrollment (including those removed from protocol) are included. Patients who died without disease progression are censored. At 4 years from enrollment, 34% have progressed and 17% have received salvage therapy for progressive myeloma. (B) Cumulative proportions of patients achieving various response levels. Included are all responses that occurred between the time of enrollment and the date of salvage therapy or the date of last contact for patients not requiring salvage therapy. Four years from study entry, 63% achieved at least 25% myeloma protein reduction (improvement, IMP); 25% qualified for having attained partial remission (PR), including 12% with near-complete remission (n-CR) and 5% with complete remission (CR). (C) Postlandmark event-free survival according to the level of response achieved within 9 months of starting thalidomide therapy. Patients attaining at least PR status had an inferior event-free survival to those achieving improvement or no improvement status; no difference was apparent between the latter 2 categories. P values are as follows: curve a versus curve b, P = .015; curve a versus curve c, P = .040; and curve b versus curve c, P = .655. (D) Cumulative proportions of patients receiving salvage therapy for myeloma progression, according to response level achieved with preceding thalidomide preemptive intervention. Patients who had attained at least PR status on thalidomide for SMM started salvage therapy for disease progression sooner and ultimately in higher proportions than those who had either not responded (no improvement) or qualified for improvement only after preemptive intervention with thalidomide. P values are as follows: curve a versus curve b, P < .001; curve a versus curve c, P < .001; and curve b versus curve c, P = .926.
54% within 2 years, mainly on account of patients’ and physicians’ choices. At 4 years from study entry, IMP, PR, n-CR, and CR were achieved in 63%, 25%, 12%, and 5% of patients, respectively (Figure 1B), with median times to response of 1 to 2 years as opposed to 1 to 2 months in the therapeutic study of THAL for advanced and refractory MM.9 We next examined the impact of the level of response to THAL within 9 months of starting therapy, when 64 subjects had not yet suffered an event, on overall survival (OS), event-free survival (EFS), and time to MM therapy (TTMT). Although OS was similar in the 3 response categories (70% estimate at 6 years), EFS was significantly shorter in patients who had achieved PR or better on THAL (Figure 1C), as was TTMT (Figure 1D). B2M elevation was significantly associated with shorter EFS, and development of CAs imparted significantly shorter TTMT in patients achieving PR or better status on THAL therapy was the only parameter significantly and independently associated with short TTMT. The unexpected shorter TTMT in patients achieving PR or better status with THAL may be explained by a high sensitivity to THAL of tumors with greater proliferative potential that ultimately, however, progress sooner due to rapidly developing resistance or tumor escape after drug discontinuation. Thus, by inducing remissions in SMM, THAL therapy identified tumors with greater propensity for progression to MM.

The median postsalvage survival of more than 5 years following preemptive THAL therapy for SMM is in line with treatment results achieved in primary symptomatic MM, alleviating concerns about THAL-induced resistance. Lenalidomide, a more potent and better tolerated THAL congener,22,23 would appear a more suitable agent to be explored for longer-term preemptive intervention in SMM. In the absence of randomized clinical trial–derived data, patients with SMM should be observed without therapy until progression or symptom development. The Southwest Oncology group is preparing a protocol that randomly assigns subjects with SMM to lenalidomide or placebo, once a smoldering course has been documented during a 3-month lead observation time. Clinical end points will be time to symptomatic disease requiring MM therapy and survival. Correlative science studies will include gene expression profiling to determine molecular subgroups24 and the presence of a MGUS-like signature.25

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Authorship
Conflict-of-interest disclosure: J.B.Z. is an employee of Celgene. All other authors declare no competing financial interests.
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