menting environmental cleaning, and excluding nonessential staff as well as visitors.

The epidemiologic investigation and phylogenetic analyses indicate that the most likely form of transmission during the outbreak was person-to-person transmission, either through respiratory droplets or through direct or indirect contact. The applied infection-control measures appeared to have been effective in averting the outbreak.

The CDC continues to recommend the use of airborne-infection isolation rooms for patients with SARS and MERS-CoV.\(^1,2\) Cohorting of patients in one floor or unit is a viable strategy to devote resources and staff to the care of patients.\(^1\) The infection-control measures applied in the Al-Hasa outbreak probably contributed to the control of the outbreak and were consistent with the World Health Organization’s interim infection-control guidance, which is based on the available scientific evidence.\(^3\)

Ziad A. Memish, M.D.
Ministry of Health
Riyadh, Saudi Arabia
zmemish@yahoo.com

Jaffar A. Al-Tawfiq, M.D.
Saudi Aramco Medical Services Organization
Dhahran, Saudi Arabia

Abdullah Assiri, M.D.
Ministry of Health
Riyadh, Saudi Arabia

Since publication of their article, the authors report no further potential conflict of interest.


DOI: 10.1056/NEJMci1311004

Treatment for High-Risk Smoldering Myeloma

TO THE EDITOR: In the study by Mateos et al. (Aug. 1 issue)\(^4\) involving patients with high-risk smoldering multiple myeloma, early treatment with lenalidomide plus dexamethasone, as compared with observation, resulted in a delay in progression to symptomatic disease and an increase in overall survival. Currently, the standard of care for patients with smoldering multiple myeloma has been observation until symptomatic disease occurs.\(^2\) Patients in the trial by Mateos et al. met at least one of two sets of inclusion criteria based on a definition of “high-risk” disease. The first set included plasma-cell bone marrow infiltration of 10% or more and a serum M-protein level of 3 g per deciliter or more.\(^3\) The second set included 95% phenotypically aberrant plasma cells in the bone marrow plasma-cell compartment detected with the use of flow cytometry as well as reductions in one or two uninvolved immunoglobulins.\(^4\) Since 40% of the patients in the trial were included on the basis of flow-cytometry criteria based on a definition of “high-risk” disease, there are some concerns regarding the generalizability of this study.

We analyzed the incidence and outcome of smoldering multiple myeloma using the Swedish Myeloma Registry, which is a prospective obser-
vational registry designed to document real-world treatment and outcomes in all patients with newly diagnosed multiple myeloma in Sweden. From January 1, 2008, through December 31, 2011, a total of 2494 patients (median age, 72 years) received a diagnosis of multiple myeloma, of whom 360 (14.4%) had smoldering multiple myeloma. Of the patients with smoldering multiple myeloma, 104 (28.8%) had high-risk disease (defined as an M-protein level of ≥3 g per deciliter and plasma-cell infiltration of ≥10%); these patients accounted for 4.2% of all patients with multiple myeloma. On the basis of the world population as reference, the age-standardized incidence of smoldering multiple myeloma is 0.44 cases per 100,000 persons, and the incidence of high-risk disease is 0.14 cases per 100,000 persons. After 2 years, 56.6% of the patients with high-risk smoldering multiple myeloma had progression to symptomatic disease, and after a median follow-up time of 29.8 months, 70.4% had progression (Fig. 1).

Given the high rate of progression observed among patients with high-risk smoldering multiple myeloma in our study, we conclude that approximately 29% of all patients with newly diagnosed smoldering multiple myeloma will be considered candidates for early treatment, according to the study by Mateos et al. There is an unmet need for a consensus definition of high-risk smoldering multiple myeloma based on prospective models that will allow for more refined incorporation of experimental treatment to clinical management of this disease.5

Sigurdur Y. Kristinsson, M.D., Ph.D.
University of Iceland
Reykjavik, Iceland
sigyngvi@hi.is

Erik Holmberg, Ph.D.
Cecilie Blimark, M.D.
University of Gothenburg
Gothenburg, Sweden

No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMc1310911

TO THE EDITOR: Mateos et al. report that early treatment with lenalidomide and dexamethasone followed by maintenance therapy with lenalidomide was superior to observation in time to progression to symptomatic disease and overall survival among patients with high-risk smoldering myeloma. Long-term lenalidomide therapy could be associated with failure of autologous peripheral-blood stem-cell collection in patients with multiple myeloma,1,2 and the International Myeloma Working Group recommends stem-cell collection within the first 4 cycles after initial therapy.3 Thus, 9 cycles of induction therapy and 15 cycles of maintenance therapy with lenalidomide might affect the stem-cell pool and interfere with collection of sufficient numbers of stem cells when patients have progression to symptomatic myeloma, for which high-dose chemotherapy with autologous peripheral-blood stem-cell transplantation is the current standard of care. We would be grateful if the authors would comment on this matter.

Kenji Tsuda, M.D.
Teikyo University Chiba Medical Center
Chiba, Japan
thedod3@hotmail.com

Tetsuya Tanimoto, M.D.
Navitas Clinic
Tokyo, Japan

Tsunehiko Komatsu, M.D.
Teikyo University Chiba Medical Center
Chiba, Japan

No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMc1310911
TO THE EDITOR: The authors attempt to answer one of the most important questions in the care of patients with myeloma: When should therapy be initiated? Although their trial shows improvement in time to symptomatic myeloma and increased overall survival with lenalidomide plus dexamethasone as compared with observation among patients with high-risk smoldering multiple myeloma, it also raises important questions regarding the clinical application of the findings. First, could some excess mortality in the observation group relate to the protocol requirement that the CRAB criteria (hypercalcemia, renal dysfunction, anemia, and bone lesions) be reached before instituting therapy in that group, whereas asymptomatic biologic progression was the trigger to reinstitute dexamethasone (and increase the dose of lenalidomide) in the intervention group? Second, how many patients in the observation group reached asymptomatic biologic progression before full CRAB progression, and when did they do so? Third, did follow-up compliance and testing intensity differ between the two groups? Although the flow cytometry–based definition of high-risk disease limits widespread implementation, this study does not allow us to clearly determine whether a preemptive strategy may be equally beneficial with less toxic effects than a prophylactic strategy in high-risk smoldering multiple myeloma.

Angela Dispenzieri, M.D.
Shaji Kumar, M.D.
Mayo Clinic
Rochester, MN
dispenzieri.angela@mayo.edu

Drs. Dispenzieri and Kumar report receiving support for clinical trials from Celgene. No other potential conflict of interest was reported.

DOI: 10.1056/NEJMc1310911

TO THE EDITOR: Mateos and colleagues describe the use of lenalidomide and dexamethasone in patients with smoldering myeloma who had an increased risk of progression to symptomatic myeloma. Although the delay in progression to symptomatic myeloma is not surprising, the striking survival advantage at 3 years makes this a potentially practice-changing study. The risk of venous thromboembolism was 5% in the treatment group (one patient was receiving aspirin, one was receiving warfarin, and one was not receiving thromboprophylaxis). In studies involving patients with myeloma who were receiving lenalidomide with varying doses of dexamethasone, the rate of venous thromboembolism is between 10 and 30%.1,2 Can the authors elaborate more on the thromboprophylaxis strategies used in their study?

Sameer Mahesh, M.D.
Summa Health System
Akron, OH
sameermahesh77@yahoo.com

No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMc1310911

THE AUTHORS REPLY: Kristinsson et al. report that of patients with newly diagnosed smoldering multiple myeloma in the Swedish Myeloma Registry, 28.8% were considered to have high-risk disease on the basis of the presence of a serum M-protein level of 3 g per deciliter or more and a proportion of plasma cells in the bone marrow of 10% or more.1 More than half of these high-risk patients (56.6%) had progression to symptomatic disease after 2 years. We agree with Kristinsson et al. that consensus is needed regarding the definition of high-risk smoldering multiple myeloma. Although several existing clinical and biologic markers predict progression from smoldering multiple myeloma to symptomatic disease,2 more sensitive and reproducible prognostic factors should be identified and incorporated into clinical practice.

Tsuda et al. question whether lenalidomide affected the ability to mobilize and collect sufficient CD34+ cells. In our study, stem-cell collection was planned after the first four cycles. Granulocyte colony-stimulating factor (at a dose of 10 μg per kilogram of body weight per day) was used as mobilizer agent, and the target number of CD34+ cells was at least 2×10^6 per kilogram. In the 21 patients identified by investigators as being candidates for autologous stem-cell transplantation, the median number of CD34+ cells collected was 3.1×10^6 per kilogram (range, 0.3 to 15.1) after a median of 2 apheresis procedures (range, 1 to 4). In two patients, the target number of CD34+ cells was not reached.
In answer to the three questions posed by Dispenzieri and Kumar: first, our protocol was consistent with current guidelines that recommend treatment of smoldering myeloma only once myeloma-related symptoms develop. The use of active treatment at the time of biologic relapse in the observation group may be an interesting preemptive strategy for future research. Second, in our study, biologic progression before full CRAB progression occurred in 12 of 62 of patients within the observation group (19%) at a median of 6.5 months from study inclusion (range, 2.0 to 21.0). Third, both groups had identical testing intensity, since all tests, including serum and urinary levels of the monoclonal component, were assessed monthly until study discontinuation.

Mahesh raises concern regarding thromboprophylaxis. Our trial imposed the thromboprophylaxis protocol recommended by the International Myeloma Working Group guidelines: aspirin for patients with one or no risk factors for venous thromboembolism, and low-molecular-weight heparin for those with more than one risk factor for venous thromboembolism. The lower incidence of venous thromboembolism in our study as compared with that in previous studies could be due to the inclusion of patients with a low risk of venous thromboembolism (with no myeloma-related symptoms, a low tumor burden, the use of low-dose dexamethasone, and no significant coexisting conditions).

Maria-Victoria Mateos, M.D., Ph.D.
Jesus-F. San Miguel, M.D., Ph.D.
University Hospital of Salamanca
Salamanca, Spain
sanmiguel@usal.es

Since publication of their article, the authors report no further potential conflict of interest.


DOI: 10.1056/NEJMc1310911

Herpes Zoster

TO THE EDITOR: In his review article on herpes zoster, Cohen (July 18 issue) reports that the live attenuated herpes zoster vaccine can be given to persons with a history of herpes zoster. However, studies have shown that the risk of a recurrence of herpes zoster in an elderly immunocompetent person is less than 1% per year, and results from a major vaccine trial in this age group led to an estimate of 0.1 to 0.2% per year through 6 years. Although the herpes zoster vaccine is safe in patients with a history of herpes zoster, Cohen provides no evidence that it further reduces the rate of recurrence or the rate of postherpetic neuralgia in this specific group. Moreover, the efficacy of the vaccine wanes over the first 5 years. Why, then, does he recommend vaccination of elderly immunocompetent patients with a well-documented history of a previous episode of herpes zoster?

Jan V. Hirschmann, M.D.
Puget Sound VA Medical Center
Seattle, WA
pepsi@u.washington.edu

No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMc1310369

TO THE EDITOR: It was surprising that Cohen does not provide interventional (i.e., injection-based) options for the treatment of pain associated with acute shingles that is unresponsive to medical therapies. Although data are lacking from randomized, controlled trials to show the benefits of such interventions, case series sug-