Prevention of Progression in Monoclonal Gammopathy of Undetermined Significance

□□ *Commentary on Golombick et al., p. 5917*

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Monoclonal gammopathy of undetermined significance (MGUS) is a common premalignant plasma cell proliferative disorder with a lifelong risk of progression to multiple myeloma. Because myeloma is an incurable malignancy, strategies to delay or prevent progression in high-risk patients are of considerable importance. (Clin Cancer Res 2009;15(18):5606–8)

In this issue of *Clinical Cancer Research*, Golombick and colleagues (1), report on preventive therapy for monoclonal gammopathy of undetermined significance (MGUS) using curcumin, the most active component of the commonly used Indian spice, turmeric. This small pilot trial uses nonstandard response criteria and does not affect clinical practice, but is an important study that raises several major issues pertinent not just to the field of plasma cell disorders, but also to the overall concepts of premalignancy and chemoprevention. To fully appreciate the implications of this research it is important to understand the nature of MGUS, and the unique biologic and clinical dilemmas posed by this entity.

MGUS is a classic premalignant condition, present in more than 3% of the general population over the age of 50 years (2). The main clinical significance of MGUS is its lifelong risk of transformation to myeloma or related malignancy, at a fixed but unrelenting rate of 1% per year (3). Because myeloma is a devastating incurable malignancy, understanding why MGUS occurs and what causes its progression is of considerable importance. Recent studies show that myeloma is almost always preceded by MGUS (4, 5), lending additional impetus for testing preventive strategies such as the one undertaken by Golombick and colleagues for patients with MGUS who are at high risk of progression.

The study by Golombick is among the first preventive studies in clinically defined MGUS, although others have used preventive strategies such as anakinra and thalidomide in a more advanced form of biologic MGUS, clinically referred to as smoldering multiple myeloma (SMM). The clinical distinction between MGUS and SMM is important for prognosis and for testing of preventive strategies, but SMM is likely not a discrete biologic entity. Most patients clinically recognized as SMM have biologic MGUS (premalignancy), whereas some likely have early stages of myeloma.

Etiologic Factors for MGUS and Prospects for Primary Prevention

Recent observations offer important clues, indicating that genetic predisposition and potentially preventable environmental factors may play a key role in the development of MGUS. African Americans, and blacks from Africa, have a two- to threefold higher risk of MGUS compared with whites (6, 7). In contrast, the risk is lower in Asians from Japan (8), and in Mexicans. Age, hormonal factors, family history, immunosuppression, and exposure to certain pesticides are known risk factors. Understanding these factors, and the pathogenetic steps discussed below may allow for the development of primary prevention strategies in the future.

MGUS is likely the culmination of a cascade of events initiated by an abnormal response to antigenic stimulation mediated by factors such as aberrant expression of Toll-like receptors (TLRs) and overexpression of interleukin 6 (IL-6) receptors (9). Any attempt at primary prevention may need to abort the abnormal response to antigenic stimulation, or perhaps the specific stimulus itself. The cascade results in the development of one of two types of primary cytogenetic abnormalities that are likely critical in establishing MGUS: hyperdiploidy or immunoglobulin heavy chain (IgH) translocations.

Implications of Discrete Cytogenetically Defined Subtypes of MGUS

Approximately 50% of MGUS is associated with hyperdiploidy (hyperdiploid or IgH nontranslocated MGUS; Fig. 1), whereas the remaining 50% is associated with translocations involving the IgH locus on chromosome 14q32 (IgH translocated or nonhyperdiploid MGUS). In a small proportion of cases, neither hyperdiploidy nor IgH translocations are found. In nonhyperdiploid MGUS, IgH translocations commonly involve one of five recurrent partner chromosome loci: 11q13 [CCND1 (cyclin D1 gene)], 4p16.3 (FGFR-3 and MMSET), 6p21 [CCND3 (cyclin D3 gene)], 16q23 (c-maf), and 20q11 (mafB; ref. 10). Although

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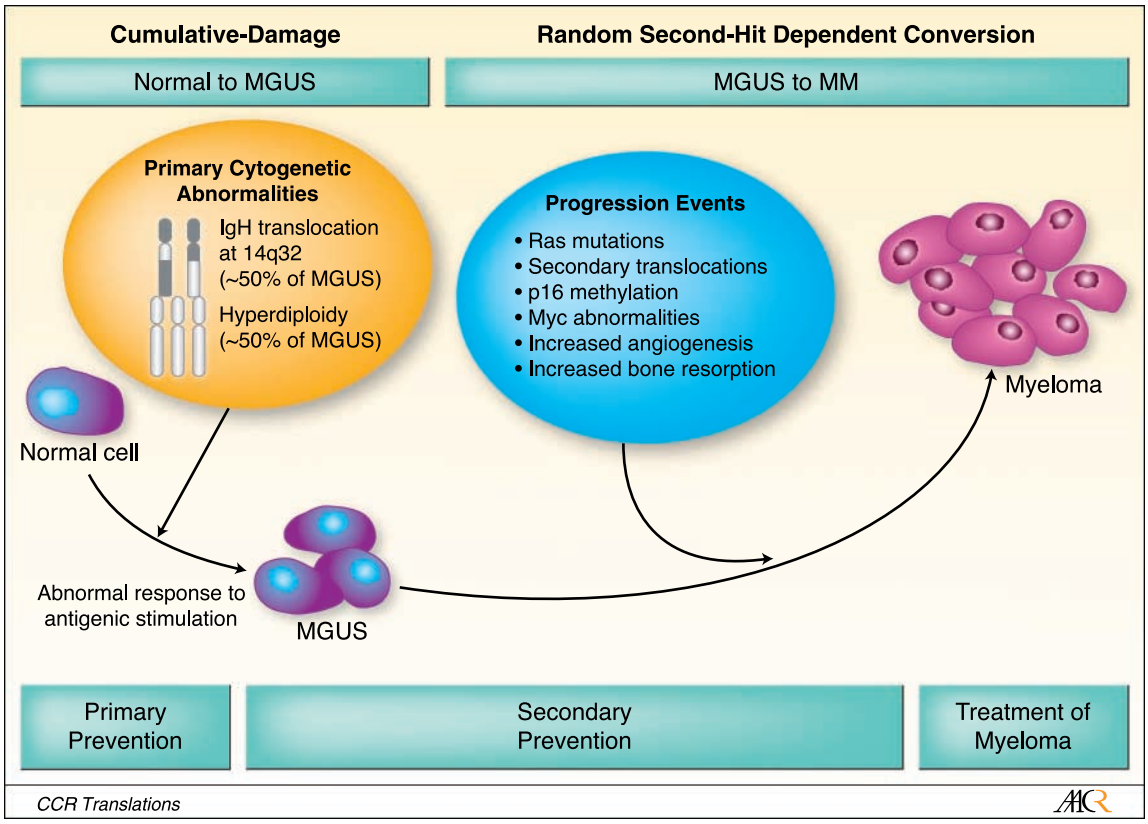

Fig. 1. Pathogenesis of MGUS and its progression to myeloma. The initiation of limited clonal plasma cell proliferation in MGUS is likely triggered by an abnormal response to antigenic stimulation in a genetically or environmentally susceptible host, and development of typical cytogenetic abnormalities, hyperdiploidy, or IgH translocations. Progression of MGUS to myeloma is accompanied by a variety of changes in the clonal cell and its microenvironment.

clinically, MGUS is considered a single entity, it is likely cytogenetically at least six different entities comprising hyperdiploid MGUS and the five most common primary IgH translocations discussed above. It is more than likely that the age and racial disparities, pathogenesis, and clinical course of these types of MGUS differ from each other. Future studies will need to examine each cytogenetic type separately.

Progression of MGUS to Myeloma and Secondary Prevention

Although the initiation of MGUS seems to follow a cumulative damage model, the progression of MGUS to myeloma suggests a simple, random, two-hit genetic model of malignancy (Fig. 1). Unfortunately, the precise mechanisms of progression are unknown, although several potentially pathogenetic abnormalities have been described; these include Ras and p53 mutations, p16 methylation, myc abnormalities, and secondary translocations. Changes in the bone marrow microenvironment include induction of angiogenesis and abnormal paracrine loops involving cytokines such as IL-6, which serves as a major growth factor for plasma cells. The main regulator of IL-6 signaling in myeloma is signal transducer and activator of transcription-3 (STAT3), and curcumin down-regulates IL-6-induced STAT3 phosphorylation. In addition, curcumin also down-regulates nuclear factor-κB (NF-κB), which is constitutively activated in myeloma cells, and felt to play a role in disease pathogenesis and drug resistance (11).

The pathogenesis of lytic bone lesions associated with progression of MGUS is unclear. There is an increase in receptor activator of nuclear factor κB ligand (RANKL)-expression by osteoblasts (and possibly plasma cells), accompanied by a reduction in the level of its decoy receptor, osteoprotegerin (OPG; ref. 12). The resultant increase in RANKL/OPG ratio causes osteoclast activation and increased bone resorption and turnover. Curcumin inhibits RANKL signaling, and in this trial Golombick and colleagues (1) were able to show a reduction in bone turnover in a subset of patients. Osteoclast activation in myeloma is also mediated by increased levels of macrophage inflammatory protein-1α (MIP-1α), IL-3, and IL-6, whereas increased levels of IL-3, IL-7, and dickkopf 1 (DKK1) inhibit osteoblast differentiation.

Clinical Implications

Any preventive strategy for MGUS, including trials with relatively nontoxic agents such as curcumin need to consider the absolute risk of progression to malignancy. The true life-time probability of progression of MGUS is substantially lower than 1% per year when competing causes of death are taken into account, approximately 11% at 25 years (13). Phase III studies with curcumin and other preventive strategies should be focused on patients who are at the highest risk of progression.

The main risk factors for progression of clinical MGUS are size and type of the serum M protein, and presence of an abnormal serum free light chain (FLC) ratio (13). An abnormal FLC ratio (especially a more extreme value) most likely derives its prognostic value by being a surrogate marker of certain cytogenetic categories, e.g., t(4;14) MGUS. Patients with an abnormal serum FLC ratio, non-immunoglobulin G (IgG) MGUS, and a high

serum M protein level (≥15 gm/L) have a risk of progression at 20 years of 58% (high-risk MGUS), compared with 5% when none of the risk factors are present (low-risk MGUS). Patients with high-risk MGUS and patients with biologic MGUS clinically identified as SMM are candidates for preventive strategies including phase III trials with curcumin.

Future Chemoprevention Trials in MGUS and SMM

With the increasing availability of novel targeted therapies for myeloma, phase III clinical trials are ongoing to determine if the early use of drugs such as lenalidomide or bisphosphonates can delay progression in MGUS and SMM. Curcumin joins the list of other potential agents that need further study. As discussed above, subsequent trials need to focus on those at the highest risk of progression. Trials should also stratify by cytogenetic subtype of MGUS and SMM. Therapeutic clinical trials in asymptomatic individuals are always a challenge, but in the right target population, they have the potential for substantial benefit.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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