improvements in outcome in patients treated with rituximab were as strong in young males as in young females with low-risk disease in the MInT study and in young poor-prognosis patients in the Mega-CHOEP trial. In contrast, in the RICOVER-60 trial, both elderly females and males benefited from the addition of rituximab, but the improvement was greater in elderly females. These data suggested that the effect was not at the level of the malignant lymphoma cell but was a pharmacokinetic one. Rituximab clearances were similar in young males and young females. Elderly females, who had the greatest benefit from rituximab, had a statistically significant slower rituximab clearance resulting in higher serum levels and longer exposure times related to an age-dependent decrease in rituximab clearance in females. The sex- and age-dependent clearance with rituximab is unusual in the field of chemotherapy drugs.

Do older males benefit from rituximab? In the RICOVER-60 trial, rituximab did improve the OS by 10%. Older males have a more rapid rituximab clearance resulting in suboptimal dosing with rituximab when dosed at 375 mg/m^2. In the smart elderly (SMARTE)-R-CHOP-14 trial, older patients received 8 doses of rituximab over 240 days resulting in a 20% improvement in poor prognosis males but only a 4% improvement in older females.[1]

Do these observations have implications for ongoing clinical trials in diffuse large B-cell lymphoma? New approaches include adding new drugs such as lenalidomide and ibrutinib to R-CHOP. The role of lenalidomide in combination with R-CHOP (R2-CHOP) in improving outcomes in patients with the activated B-cell signature is currently under evaluation in a randomized phase 2 intergroup study. The influence of the outcomes in elderly male patients in this study, the ibrutinib studies, and maintenance rituximab studies will be essential to understand.

The cutoff of age 60 has been used to define elderly as initially described in the IPI by the International Non-Hodgkin's Lymphoma Prognostic Factors Project.[2] Ongoing studies suggest that there are differences in outcomes in patients age 60 vs age 70. Variables are dichotomous in the IPI model. Models using multicategorical predictors with age as a continuous variable might further refine risk prediction in populations and for individual patients and enhance interpretation of clinical trial results. The term elderly has been incorporated into clinical trials. The field would be well served to move away from the term elderly.

The importance of the contributions of Pfreundschuh and colleagues cannot be underestimated. The opportunity to combine large data sets of well-defined patients is invaluable when attempting to address these types of questions. The utilization of resources to store peripheral blood samples, to have patients consent to pharmacologic studies, to perform the studies, and to assemble the team to analyze the data is a model for future studies. The collection of peripheral blood with storage of serum, plasma, cells, DNA, and RNA is even more important in the genomic era. Twenty years later, we still continue to learn more about rituximab. This report demonstrates the importance of pharmacokinetic studies in all potential ages and both sexes. The optimal dose and schedule for rituximab will be related to pharmacokinetic-based investigations in studies of patients in different age groups and different sexes

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● ● ● CLINICAL TRIALS & OBSERVATIONS

Comment on Farr et al, page 647

Less strength and more fractures for MGUS bones

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In this issue of *Blood*, Farr et al showed that patients with monoclonal gammopathy of undetermined significance (MGUS) have increased cortical bone porosity and reduced bone strength,[1] conditions that can lead to the increased fracture risk, which has been reported in MGUS patients.[2]

The importance of understanding the mechanisms of bone loss in MGUS is of extreme value as the majority of these patients do not receive any bone targeted therapy, despite their twofold higher tendency to develop fractures, mainly in the axial skeleton, compared with age- and gender-matched controls.[2] Furthermore, these mechanisms will allow us to uncover the best imaging technique for the early depiction of bone

damage in MGUS patients. Bone densitometry assessed by dual-energy X-ray absorptiometry (DXA) scan is a noninvasive quantitative method for the assessment of fracture risk in osteoporosis. Nevertheless, DXA visualizes bones as a 2-dimensional image and offers almost no information for the 2 factors that determine bone strength: bone material composition and bone structural design.

All fractures do not have the same pathogenesis or the same structural abnormalities that increase bone fragility. There are fractures that are associated with reduced bone mineral density (BMD) and others that are associated with reduced density of osteocytes, the key cell of bone remodeling.[3] Patients who develop fractures may have different rates of bone remodeling that ranges from high to normal or low rates of remodeling. The heterogeneity of these mechanisms supports the notion that patients with fractures should not be treated in a similar way. Moreover, bone fragility is influenced by biomechanical parameters, such as the ultimate force, ultimate displacement, and energy absorption.[3] However, what is happening in the bones of MGUS patients? Are there differences between patients with MGUS who develop fractures and those who do not? First of all, in the biochemical level, we know that MGUS patients have elevated bone resorption, assessed by the increased levels of N-telopeptide of collagen type I, one of the most accurate markers of bone resorption. This increase reflects the increased osteoclastic activity, which is driven by the elevation of the ratio of the major osteoclastogenesis factor, the receptor activator of nuclear factor κ-B ligand (RANKL) to osteoprotegerin (OPG).[4] Indeed, the sRANKL/OPG ratio is higher in MGUS patients with fractures compared with those without fractures.[5] Furthermore, circulating levels of dickkopf-1 are high at least in subsets of patients with MGUS, suggesting a bone formation inhibitory effect on these patients.[6] MGUS patients with fractures are usually older (mean age, 63 years), with longstanding disease (>8 years) compared with those without fractures (60 years and 6 years after diagnosis), whereas their BMD of the lumbar spine, femoral neck, and total BMD is lower,[5] and this is one of the main reasons of increased bone fragility in MGUS. High-resolution peripheral quantitative computed tomography (HRpQCT) volumetric BMD (vBMD) confirms the presence of alterations in the bone microarchitecture of MGUS patients.[6]

The reason for this defect is unknown to date. Axial skeleton is the major area of fractures in MGUS and cortical bone comprises approximately 80% of the axial skeleton or even more after the age of 65 years when MGUS is more prevalent. Cortical thinning and porosity reduces the resistance of bone to the propagation of cracks, initially by the development of microcracks and then by complete fractures.[7] On the contrary, bone formation and the deposition of new bone reduces cortical porosity and focal stress, thereby preventing bone microdamage. The importance of cortical thinning and porosity in the fracture risk is reflected by the notion that a reduction of 1 standard deviation in cortical thickness is associated with a nearly threefold increased risk of fracture in healthy population.[8] In the present brief report, the Mayo Clinic group used HRpQCT of the radius in 50 MGUS patients and 100 controls and showed that MGUS patients have higher cortical porosity with higher cortical pore volume and low vBMD compared with controls. Moreover, all parameters of bone strength (ie, failure load and stiffness) and mainly apparent modulus were lower in MGUS patients. Thus, this report reveals at least 2 major mechanical reasons for increased fragility in the bones of MGUS patients: increased cortical thinning and reduced bone strength. However, the report has some limitations: (1) the low number of patients cannot allow detection of differences between MGUS patients with and without fractures; (2) the lack of follow-up does not reveal the time of these bone microarchitecture alterations; and (3) the HRpQCT needs to be tested in other areas outside the radius. The International Myeloma Working Group (IMWG) suggests that the DXA scan should be considered for patients with MGUS due to the well-documented increased fracture risk in these patients.[9] HRpQCT seems to be a valuable technique that may substitute the DXA scan in the future or give supplementary information in an attempt to recognize earlier MGUS patients with bone loss. However, this has to be proven in larger studies.

The IMWG also suggests bisphosphonates in all MGUS patients with proven osteopenia or osteoporosis.[9] Indeed, bisphosphonates increase bone strength through decreasing bone turnover. This lower bone turnover results in a higher mineralization and lower number of active resorption pits within bone. The mechanisms of bone loss described in this report support the use of bisphosphonates in MGUS patients. Bisphosphonates have been used in MGUS patients and have increased the BMD of the patients, but we do not know if they manage to reduce the number of fragility fractures.[10] If bisphosphonate therapy has to be given in all MGUS patients with HRpQCT alterations is unclear to date; further, the duration and frequency of bisphosphonates administration in MGUS patients has to be determined in large prospective studies.

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