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Is rituximab one for all ages and each sex?

Thomas M. Habermann

In this issue of Blood, Pfreundschuh et al report that young males treated with rituximab-based immunochemotherapy in contrast to elderly males benefit as much as females from rituximab immunochemotherapy and patients with more rapid rituximab clearance have reduced therapeutic benefit.

In 1993, the International Prognostic Factor Index (IPI) defined a predictive model for aggressive non–Hodgkin lymphoma. In 1993, 2 studies were designed in international cooperative groups to evaluate the role of a targeted anti–CD20 monoclonal antibody, rituximab, at a dose of 375 mg/m², in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in patients age 60 or greater with aggressive lymphoma each administered over 21 days. This was after only extremely preliminary observations of responses in data on a small number of patients who had responded to single-agent rituximab therapy after relapse from different approaches and an ongoing phase 2 study. An international trial was also undertaken in younger patients, the MabThera International Trial (MiT). The initial rituximab–CHOP (R–CHOP) regimens were empirically designed. These trials were designed without a pharmacologic understanding of rituximab or the half-life of the drug. The outcomes of these trials reported an improved overall survival (OS) when compared with CHOP or CHOP–like regimens and led to the approval of rituximab in combination with CHOP in the United States in February 2006 and in countries worldwide. This was the first monoclonal antibody approved in diffuse large B–cell lymphoma. The publication by the Groupe d’Etude des Lymphomes de L’Adulte was a landmark observation. Clinical trials incorporating rituximab into other investigations including the rituximab with CHOP over the age of 60 (RICOVER-60) and the Mega–CHOP plus etoposide (CHOP-E) trials were performed. Following the reports of the initial phase 3 trials, data emerged that females had better outcomes when treated with rituximab than males. In the rituximab era, male sex became a more adverse prognostic factor. These differences were not related to the doses of myelosuppressive drugs or rituximab received in treatment arms between men and women. In the RICOVER-60 trial, male sex was a significant risk factor for event–free survival and progression–free survival in patients treated with R–CHOP.

In this analysis, clinical data were used from 6 prospective clinical trials and pharmacokinetic studies from 49 patients on 3 clinical trials, 20 previously reported. The

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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 of rituximab when dosed at 375 mg/m². 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 Pfundenschuh 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. Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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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. Furthermore, these mechanisms will allow us to uncover the best imaging technique for the early depiction of bone
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