previously used to monitor age-associated changes in the B-cell repertoire.[3,5] Results indeed suggested that depletion of long-lived, antigen-experienced B cells in old 3-83Tg mice can, by reactivating B lymphopoiesis, give rise to a more young mouse-like repertoire.

One of the most biologically important aging-associated changes in the immune system is the failure to mount protective antibody responses on vaccination or infection by newly encountered pathogens.[7] To test the competence of the rejuvenated peripheral B-cell compartment, the authors immunized aged mice that had been subjected to B-cell depletion. They observed a significant increase in the ability of the mice to mount a primary antibody response, although these responses were much reduced compared with those of young mice.

Rejuvenation by peripheral B-cell depletion is at odds with previous experiments in which hematopoietic stem cells from aged animals failed to reconstitute a young-like repertoire when transferred to lethally irradiated, therefore B cell–depleted, young recipients.[5] In these earlier studies, it was further shown that simple reduction of the number of young HSCs transferred to irradiated recipients replicated the defect. This pointed to low frequency of lymphoid-competent HSCs in the old bone marrow as an underlying cause of the defect. Recent studies have shown that HSC populations may be composed of functionally distinct subsets characterized by distinct differentiation potential[8-11] and that this composition is altered during aging with expansion of myeloid-biased HSCs.[12] Thus, multiple factors are at play in aging-associated immuno-senescence.

A remaining question is explanation of the observed selective loss of B- versus T-lymphopoietic potential in HSCs from aged animals. Provided the thymus is functional, T lymphopoiesis is retained.[5] Thus, immunologically aged progenitors seem to display a specific defect in B-cell production rather than a simple skewing of myeloid- and lymphoid-biased cells. Might the cross-talk observed by Keren et al contribute to this bias?

The findings of Keren et al are important in showing that defective B lymphopoiesis in aging may be partially reversed and that peripheral B-cell populations can speak to the lymphopoietic machinery. It is tempting to speculate about the existence of a soluble factor secreted in the periphery and sensed at the hematopoietic progenitor level. The next step will be to explore the nature of this activity.

Keren and colleagues' work may constitute a breakthrough in our understanding of the molecular basis of the age-associated immune dysfunction. Of import to the common man is the possibility the clinical depletion of the source of this repressive activity may increase immune function in the aged.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

REFERENCES

1. Keren Z, Naor S, Nussbaum S, et al. B-cell depletion reactivates B lymphopoiesis in the bone marrow and rejuvenates the B lineage in aging. *Blood*. 2011;117(11):3104-3112.
2. Kline GH, Hayden TA, Klinman NR. B cell maintenance in aged mice reflects both increased B cell longevity and decreased B cell generation. *J Immunol*. 1999;162(6):3342-3349.
3. Johnson SA, Rozzo SJ, Cambier JC. Aging-dependent exclusion of antigen-inexperienced cells from the peripheral B cell repertoire. *J Immunol*. 2002;168(10):5014-5023.
4. Rossi DJ, Bryder D, Zahn JM, et al. Cell intrinsic alterations underlie hematopoietic stem cell aging. *Proc Natl Acad Sci U S A*. 2005;102(26):9194-9199.
5. Guerrettaz LM, Johnson SA, Cambier JC. Acquired hematopoietic stem cell defects determine B-cell repertoire changes associated with aging. *Proc Natl Acad Sci U S A*. 2008;105(33):11898-11902.
6. Mayack SR, Shadrach JL, Kim FS, Wagers AJ. Systemic signals regulate ageing and rejuvenation of blood stem cell niches. *Nature*. 2010; 463(7280):495-500.
7. Lu YF, Cerny J. Repertoire of antibody response in bone marrow and the memory response are differentially affected in aging mice. *J Immunol*. 2002;169(9):4920-4927.
8. Dykstra B, Kent D, Bowie M, et al. Long-term propagation of distinct hematopoietic differentiation programs in vivo. *Cell Stem Cell*. 2007;1(2):218-229.
9. Sieburg HB, Cho RH, Dykstra B, Uchida N, Eaves CJ, Muller-Sieburg CE. The hematopoietic stem compartment consists of a limited number of discrete stem cell subsets. *Blood*. 2006;107(6):2311-2316.
10. Wilson A, Laurenti E, Oser G, et al. Hematopoietic stem cells reversibly switch from dormancy to self-renewal during homeostasis and repair. *Cell*. 2008;135(6):1118-1129.
11. Challen GA, Boles NC, Chambers SM, Goodell MA. Distinct hematopoietic stem cell subtypes are differentially regulated by TGF-beta1. *Cell Stem Cell*. 2010;6(3):265-278.
12. Beerman I, Bhattacharya D, Zandi S, et al. Functionally distinct hematopoietic stem cells modulate hematopoietic lineage potential during aging by a mechanism of clonal expansion. *Proc Natl Acad Sci U S A*. 2010;107(12):5465-5470.

● ● ● CLINICAL TRIALS

Comment on Gay et al, page 3025

Toward deeper response in MM

Joan Bladé and Carlos Fernández de Larrea HOSPITAL CLÍNIC, BARCELONA

In this issue of *Blood*, Gay and colleagues report that in 1175 elderly myeloma patients treated with melphalan/prednisone plus novel agents, the achievement of complete remission was an independent predictor of outcome.[1]

Multiple myeloma (MM) is a proliferation of clonal bone marrow plasma cells (BMPCs) characterized by a high degree of resistance to chemotherapy. In fact, complete remission (CR) was rarely observed with the use of conventional chemotherapy. For many years stabilization of tumor load was considered a more powerful prognostic factor than degree of tumor reduction.[2] More recently, it was shown that high-dose therapy followed by autologous stem-cell transplantation (ASCT) results in a higher tumor reduction, and a significant correlation between the degree of tumor decrease and survival was observed. This lead to the definition of CR by the European Blood and Marrow Transplantation (EBMT) group as negative immunofixation electrophoresis (IFE) in serum and urine, in the absence of increased BMPCs. More recently, the International Myeloma Working Group (IMWG) expanded the CR EBMT criteria by adding the category of stringent CR (sCR), defined by negative IFE in serum and urine with a normal serum free light chain (FLC) ratio plus the absence of clonal BMPCs by immunohistochemistry or immunofluoresce.[3] The IMWG also introduced the concept of very good partial response (VGPR; ≥ 90% M-protein decrease) as a separate category of partial response (PR; ≥ 50% M-protein decrease). In addition to the EBMT and IMWG response criteria, the achievement of negative minimal residual disease (MRD) by multiparameter flow cytometry (MFC)[4] or by molecular studies[5] are essential for long-term remission duration and prolonged survival. Finally, between 10% and 40% of patients with MM in CR after ASCT develop oligoclonal bands, a fact likely resulting from a robust humoral response and associated with a favorable outcome.[6]

For many years the gold standard for patients with MM not eligible for ASCT has been the combination of melphalan and prednisone (MP) or dexamethasone-based regimens. The overall response rate was < 50% with a CR rate of < 5%, a median duration of response of 1.5 years, and a median overall survival (OS) of ~ 3 years. Interestingly, for this population of patients, new combination regimens incorporating novel drugs such as MP-thalidomide (MPT), MP-bortezomib (MPV), MP-lenalidomide (MPR), or lenalidomide plus dexamethasone have resulted in an unprecedented CR rate of up to 15%, 30%, 24%, and 24%, respectively.[7] However, the impact of these CRs on event-free survival (EFS) and OS in the nontransplantation setting has not yet established.

In this issue of *Blood*, Gay et al report on the impact of response to therapy on progression-free survival (PFS) and OS in 1175 newly diagnosed patients with MM, not eligible for ASCT and enrolled in 3 multicenter trials, treated with either MP alone (332), MPT (332), MPV (235), or MPV followed by VT maintenance (254).[1] Concerning response, CR was achieved in 17%, VGPR in 19%, and PR in 35%. According to the treatment group, CR was attained in 49%, 31%, 15%, and 5% of patients treated with MPV-VT, MPV, MPT, and MP, respectively. After a median follow-up of 29 months, PFS and OS were significantly longer in patients who achieved CR versus those who attained VGPR or PR. Of interest, the PFS and OS were virtually identical in patients who achieved VGPR and PR. Finally, the achievement of CR was an independent predictor of longer PFS and OS irrespective of age, International Staging System stage, and treatment arm.

There is no doubt that, in the transplantation setting, the achievement of IFE-negative CR is a crucial step forward for long-lasting response and survival in MM.[8] Gay et al clearly demonstrate that the achievement of IFE-negative CR in elderly patients treated with MP plus novel antimyeloma agents has also a significant impact on PFS and OS.[1] Interestingly enough, in a recent transplantation series, the achievement of VGPR did not result in a better outcome than the achievement of PR.[9] It has been shown that approximately one-third of CRs achieved after ASCT in younger myeloma patients last for > 10 years, representing the so-called "cure fraction" or "operational cure."[8] Although the achievement of a PFS of 67% at 3 years in elderly patients with MM in the study of Gay et al is encouraging,[1] it must be considered that the follow-up is still too short with few patients at risk beyond 4 years from initiation of therapy, to know whether or not operational cures can be expected with primary therapy incorporating novel agents in elderly patients. Furthermore, with the availability of novel technologies, the achievement of IFE-negative CR should no longer be the ultimate goal in the treatment of MM. In this regard, the impact of sCR should be investigated. It has been recently reported that the achievement of CR with primary therapy including novel agents results in the emergence of oligoclonal bands in up to 60% of the patients.[10] Whether this phenomenon is because of a higher tumor reduction or a more robust immune reconstitution as well as its potential prognostic influence are unknown. Finally, sequential MRD measurements with MFC or molecular studies could be helpful in determining from what level of MRD further treatment is or not needed. Ideally, the treatment approach in elderly patients with MM should include a triple-agent induction regimen such as MPT or MPV followed by maintenance incorporating novel agents along with sequential MRD studies to establish for how long treatment is still of benefit.

Conflict-of-interest disclosure: J.B. has received honoraria for consultation, educational lectures, and research grants from Celgene and Janssen-Cilag. C.F.d.L has received honoraria for educational lectures from Janssen-Cilag. ■

REFERENCES

1. Gay F, Larocca A, Wijermans P, et al. Complete response correlates with long-term progression-free and overall survivals in elderly myeloma treated with novel agents: analysis of 1175 patients. *Blood*. 2011;117(11):3025-3031.

2. Bladé J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol*. 1998;102(5):1115-1123.

3. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1467-1473.

4. Paiva B, Vidriales MB, Cerveró J, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. *Blood*. 2008;112(10):4017-4023.

5. Ladetto M, Pagliano G, Ferrero S, et al. Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. *J Clin Oncol*. 2010;28(12):2077-2084.

6. Fernández de Larrea C, Cibeira MT, Elena M, et al. Abnormal serum free light chain ratio in patients with multiple myeloma in complete remission has strong association with the presence of oligoclonal bands: implications for stringent complete remission definition. *Blood*. 2009;114(24):4954-4956.

7. Bladé J, Cibeira MT, Rosiñol L. Novel drugs for the treatment of multiple myeloma. *Haematologica*. 2010;95(5):702-704.

8. Bladé J, Rosiñol L, Cibeira MT, Rovira M, Carreras E. Hematopoietic stem cell transplantation for multiple myeloma beyond 2010. *Blood*. 2010;115(18):3655-3663.

9. Lahuerta JJ, Mateos MV, Martínez-López J, et al. Influence of pre- and post-transplantation responses on outcome of patients with multiple myeloma: sequential improvement of response and achievement of complete response are associated with longer survival. *J Clin Oncol*. 2008;26(35):5775-5782.

10. Fernández de Larrea C, Tovar N, Cibeira MT, et al. Emergence of oligoclonal bands in patients with multiple myeloma in complete remission after induction chemotherapy: association with the use of novel agents. *Haematologica*. 2011;96(1):171-173.

● ● ● LYMPHOID NEOPLASIA

Comment on Baraniskin et al, page 3140

PCNSL: biomarker better than biopsy?

Gerald Illerhaus and Tracy Batchelor UNIVERSITY HOSPITAL FREIBURG; MASSACHUSETTS GENERAL HOSPITAL

In this issue of *Blood*, Baraniskin and colleagues report on microRNAs (miRNAs) as a possible biomarker for the diagnosis of primary central nervous system lymphoma (PCNSL).[1] Levels of *miR-21, miR-19, and miR-92a* were significantly increased in cerebrospinal fluid (CSF) samples from PCNSL patients compared with controls with inflammatory CNS disease or other neurologic disorders.

The diagnosis of PCNSL is most commonly achieved via stereotactic brain biopsy. Contemporary imaging methods (CT, MRI, PET) fail to reliably differentiate inflammatory processes, solid-tumor metastases, and primary or secondary CNSL. A misinterpretation of findings can lead to a delay in initiating therapy on the one hand, or to unnecessary