that contrary to common belief, this senescence is independent of the cell-cycle regulators p16 and Arf, proteins prominently involved in replicative senescence and DNA damage checkpoint activation, as well as stem cell aging. These results thus imply that changes in these cell-cycle regulators are rather correlative and not primarily causative for regulation of hematopoiesis in response to TBI. This manuscript thus greatly extends our current knowledge on the long-term effects of DNA damage on hematopoiesis and hematopoietic stem cells.

What do these results mean for the clinic? Because of the success of DNA-damaging treatments in various cancer settings, and because of the demographic changes in our society, we will most likely see more patients who have received such therapies. One might need to be more vigilant with respect to undetected bone marrow injury in such patients.

Where do we go from here in research? One question always linked to DNA-damaging regimens is the question on DNA mutations in response to the damage. Is senescence and the following reduced clonogenicity protecting the hematopoietic system from acquiring a set of actively cycling but mutated stem cells? Does radiation damage support therapy, either via high levels of cytokines or via radioprotective or radiomimicking treatments, have either a beneficial or a rather detrimental effect with respect to inducing senescence and thus long-term support of hematopoiesis? And ultimately, which cell-cycle control pathways do stem cells use to react to radiation damage and to regulate DNA-damage outcomes? And might there be a way to revert the long-term senescence associated with TBI?

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Comment on Martinez-Lopez et al, page 3073

Down to the bitter end

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“The daintiest last, to make the end most sweet,” comes to us from Shakespeare’s Richard II, but in the most recent edition of Blood, the paper from Martinez-Lopez et al1 suggests that by using minimal residual disease (MRD) testing by sequencing, we may be nearing the “end most sweet” or, in 21st century vernacular, the cure of myeloma.

The eventual goal of curing myeloma is dependent upon a number of different factors including genetic subtype (biology of the tumor), aggressiveness of treatment (biology of the physician), and the ability of the host to tolerate the prescribed treatment (biology of the patient). To date, there has been much debate and consternation around the cure vs control discussion.2 In this scenario, the forces of gentle less-intensive treatment have been satisfied to treat in a sequence of drug after drug in the name of “doing no harm.” In the paper by Martinez-Lopez et al1, it is clear that perhaps we are closer to the “sweet end” than we had previously understood. These investigators demonstrate that there may be cohorts of patients in whom detectable disease at a much lower level of detection (10−5) can be eliminated and that achieving this goal results in improved overall survival for patients. This concept of pushing therapy is an important one, and it is one that represents the first steps toward a cure for myeloma, but what does the sequencing approach for MRD testing offer that polymerase chain reaction (PCR) or multiparameter flow cytometry (MFC) does not? For starters, PCR analysis is not broadly applicable due to technical issues, and whereas it can detect MRD levels of 10−5, it does not represent a practical solution, because often only 75% of patients can have the specific primers created for subsequent testing.3 MFC is effective at similar levels of detection,3 but the methodology is in constant evolution and, on a practical basis, may not be useful outside of specialized centers due to its complexity. Most would agree that at its best, MFC can detect an MRD level of around 10−4. However, in retrospective analyses, it is clear that MRD negativity by MFC is the single most important predictor of long-term outcome following autologous transplant.5 Interestingly, using MRD testing may explain why patients with high-risk myeloma achieve conventional complete response (CR) at the same frequency as patients with standard-risk myeloma, because high-risk patients fail to achieve MRD-negative CR at a much higher frequency than their standard-risk colleagues.6 Although the platform used in the current paper did not allow MRD assessment to its optimal level of 10−6 due to the technical limitations of using stored samples, nonetheless, sequencing can measure depth of response at least 1 log lower than MFC. Additionally, the use of sequencing technology for MRD detection adds an additional advantage. Sequencing provides the clinician with a window into the biology of the remaining tumor cells. Through sequencing, not only do we know that disease is present, but also we can identify what the potential mutations are in the residual disease and use this information to target “add on” strategies to further drive disease burden down. No longer...
are we left to guess, “Which drug should I add?” We now have the potential to add in an agent that is specific for whatever is left. This is a huge step forward for the field and one that promises not only to increase the fraction of patients who achieve MRD negativity but also to ultimately increase the fraction of patients that are cured.

However, to date, most patients who achieve a CR, even MRD-negative CR, will continue to relapse. What is the limitation that these 3 methodologies share? They are all dependent upon measurement of disease burden at the site of marrow collection, and although this is a common source of disease when we are dealing with higher levels of residual disease, it does not represent the only site of potential disease. It has been shown by Barlogie and colleagues that even among patients who achieve a CR, there can be focal bone lesions that continue to harbor active disease,7 and if they are not in the pelvis, then it is possible they will be missed no matter which sensitive MRD analysis method is used. Although we have been fortunate in myeloma to have a biomarker of activity, the paraprotein, which sensitive MRD analysis method is used.

Although we have been fortunate in myeloma to have a biomarker of activity, the paraprotein, it is increasingly clear that we will need to incorporate more than radiographs in our diagnostic toolbox as we seek the cure for myeloma.8 Rather than being satisfied with an MRD-negative marrow by whatever test, imaging that is able to correctly identify the remaining areas of active bone disease is of critical importance if we are to eliminate all signs of residual disease. Thus, although sequencing or MFC is critical to assessing marrow-based disease, ultimately they need to be coupled with positron emission tomography/computed tomography imaging to demonstrate a true CR. Once the myeloma and oncology community incorporate both imaging and high-resolution sequencing technology to eliminate the last few remaining cells, we will be much closer to the bitter end of myeloma and a cure for our patients.

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Comment on Tai et al, page 3128

Engineering more efficacious antibody therapy for myeloma

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In this issue of Blood, Tai et al describe a novel monoclonal antibody (mAb) for myeloma, which is both glycoengineered and conjugated to a cytotoxic agent. This mAb targets B-cell maturation antigen (BCMA) and has considerable preclinical activity, thus holding therapeutic promise. The outlook for myeloma patients has greatly improved over the past decade with the introduction of a number of novel agents. However, there is still a significant unmet need because many patients with gene expression profiling–defined good-risk disease eventually relapse and high-risk myeloma has poor long-term disease-free survival in the majority of patients.1

Abs work through completely different mechanisms of action compared with currently available antimyeloma drugs and could complement their action at all stages of therapy. A prime example of a highly active mAb is rituximab, which has made a major impact on the management of non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Waldenstrom macroglobulinemia. However, its target, CD20, is expressed by only 15% to 20% of myeloma patients belonging to the CD2 molecular subgroup and rituximab has limited activity in this setting. A number of mAbs are in various stages of development for myeloma. These mAbs have assorted mechanisms of action and target the myeloma cell directly, induce immune responses, inactivate mediators of bone disease, neutralize growth factors, activate death receptors, and inhibit proangiogenic molecules. Promising mAbs for myeloma include the anti-CSI1 antibody, elotuzumab, and the anti-CD38 mAb, daratumumab. Elotuzumab is in phase 3 trials in both the newly diagnosed and relapsed setting, and daratumumab has demonstrated single-agent activity in early studies.

Antibody-drug conjugates (ADCs) enhance the efficacy of native mAbs by delivering a cytotoxic agent directly to tumor cells. Brentuximab vedotin is the first US Food and Drug Administration (FDA)–approved novel agent for Hodgkin disease in over 30 years and induces impressive and durable responses in relapsed disease. Brentuximab also has significant activity in anaplastic large-cell lymphoma. Tai et al report that the humanized, antagonistic mAb, J6M0 (GSK2857916), which is directed at BCMA, has impressive activity both in vitro against myeloma cell lines and autologous primary myeloma as well as in mouse models.1 BCMA
Down to the bitter end

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