of BV efficacy assessment in relapse/refractory T- and B-cell lymphomas. Although the subset of patients with PTCL is quite small (n = 34) compared with previous phase 2 studies with pralatrexate (n = 115) or romidepsin (n = 131), and BV in Hodgkin lymphoma (n = 102) or ALC (n = 58), the overall and CR rates (41% and 23%, respectively) in this relapse/refractory setting are of utmost interest. As with other drugs, PFS and duration of response were short (around 6 months). In addition, no unexpected or unmanageable toxicity was observed with neutropenia, and peripheral neuropathy was the most frequent adverse event as previously described with BV.

In line with previous reports with BV or other ADC, no correlation was found between CD30 expression at the tumor cell surface and clinical response. This emphasizes that selection of patients based only on quantitative antigen assessment on tumor cells is not mandatory. Several explanations have been proposed to elucidate this apparently paradoxical lack of correlation between ADC potency and target expression. A homogeneous expression of the targeted antigen does not seem a prerequisite for efficacy. Further mechanistic studies are warranted to fully understand such a lack of correlation.

The high potency and low toxicity of BV reported in the present study shed light on the possibility of combining the drug with conventional chemotherapy both in de novo and in relapse/refractory disease. However, a formal warning by the FDA was emitted concerning the use of BV and bleomycin due to a high rate of pulmonary toxicity. A phase 3 trial comparing BV-AVD (doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD] without bleomycin) and ABVD is currently proceeding (NCT01712490).

Similarly, a phase 3 randomized trial (NCT01777152) comparing CHOP vs BV-CHP (CHOP without oncovin) for patients with de novo CD30+ PTCL is ongoing. In the near future, such combinations of BV with CHP in first line or with bendamustine in second or subsequent lines of treatment (and as a bridge toward stem cell transplant in some cases) might therefore refine the poor prognosis of these PTCL patients with a high unmet medical need.

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Comment on Shao et al, page 3105

HSC senescence upon irradiation

Hartmut Geiger1,2 1ULM UNIVERSITY; 2CINCINNATI CHILDREN’S HOSPITAL MEDICAL CENTER

In this issue of Blood, Shao et al report that a side effect of total body irradiation (TBI) is long-term bone marrow injury and thus dysfunctional hematopoiesis caused by the induction of hematopoietic stem cell (HSC) senescence. Interestingly and unexpectedly, however, this happens in a manner independent of the cell-cycle regulators Ink4a and Arf, which play a major role in senescence in other cell systems.

Treatment of cancer with radiation or chemotherapeutic regimens is a success-story for patients. The refinement of these regimens, in combination with novel targeted therapies, has led to a marked increase in long-term survival, which then renders the question of long-term side effects of such therapies as clinically more relevant. So what are long-term consequences and thus likely side effects on hematopoiesis and function of hematopoietic stem cells in response to, for example, radiation treatment? This question usually focuses on the accumulation of DNA damage upon treatment and the likely contribution of DNA mutations resulting from that treatment to therapy-related myelodysplastic syndrome or therapy-related acute myeloid leukemia. Conversely, bone marrow suppression, which is still a very common side effect of radiotherapy and still an important cause of death after exposure to a moderate or high dose of TBI, has not been studied in great detail thus far in the clinical setting or animal model systems, especially in the context of long-term outcomes and consequences for stem cells. This is why this novel study of Shao et al is so important.

Based on previously published data from this laboratory, in which they identified that early hematopoietic progenitors undergo senescence in response to irradiation, they determined the long-term consequence of TBI on hematopoietic stem cells. They now provide clear evidence that long-term HSCs retain a kind of memory of irradiation damage via induction of premature senescence, which might be the underlying cause of how TBI causes long-term bone marrow suppression. Senescence induction was associated with a significant increase in the production of reactive oxygen species. This aspect of TBI has been somewhat neglected in clinical and basic research. A novel and rather unexpected, but important, additional finding is...
that contrary to common belief, this senescence is independent of the cell-cycle regulators p16 and p19, 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 radiomitting 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

Sagar Lonial1 and Charise Gleason1

1 EMMORY UNIVERSITY SCHOOL OF MEDICINE

“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. 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 al, 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^-6) 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^-6, it does not represent a practical solution, because often only 75% of patients can have the specific primers created for subsequent testing. MFC is effective at similar levels of detection, 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^-5. 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. 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. 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.
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