cells, irrespective of diagnostic leukemia antigen profiles, the LAIPs. In 2003, Rubnitz noted that the data reported by Loken and colleagues found MRD only in 16% of patients after induction. Although they demonstrated clinical significance of MRD, only one-third of relapses could be predicted. The question was whether their methodology was to be blamed. Despite improved sensitivity in the current study, again only 25% of hematologic remitters had MRD and only 2 of them (4%) presented with MRD of < 0.1%. Surveying the literature, I noted that in AML, MRD was most frequently dichotomized as positive or negative using a threshold of < or ≥ 0.1%, compared with < or ≥ 0.01% in ALL. These cut-off levels for prognostic MRD in ALL,1,6-8 versus AML,1,2,3,8-10 have been confirmed by both LAIPs and “different-from-normal” flow cytometric MRD assays.

Data from two (of the few reported) MRD-directed trials performed by St Jude Children’s Hospital7,9 suggest that differences in MRD between AML and ALL are not limited to prognostic thresholds. Their MRD-guided response data also serve as a cautionary note regarding the translatability of retrospectively obtained MRD cut-off levels to the clinic. So what are the differences between the significance of MRD in these prospective AML,9 and ALL7 trials and the retrospective AML data by Loken et al?1 (1) Loken et al identified standard-risk AML patients, based on genetic features, as those benefiting the most from MRD determinations, while MRD was not a predictor of relapse in the favorable-risk group. In the St Jude AML trial, MRD after 1 induction course was the only significant adverse prognostic factor for survival, although this effect was restricted to high-risk patients and did not affect the favorable- or standard-risk group. These observations reflect an improved outcome of standard-risk AML when postinduction therapy is intensified in response to MRD. In ALL, MRD-based risk classifications clearly outweigh established prognostic factors, including favorable-risk genetics.1,2 (2) In the trial by Loken et al, patients with MRD > 0% to < 1% and those with > 1% after the first course of induction had similar relapse-free survival, which was significantly worse than that of MRD-negative patients. Yet in the St Jude AML trial, patients who had low-level MRD after first induction (0.1% to < 1%) did as well as the MRD-negative cohort and significantly better than patients with high-level MRD (≥ 1%).9 This therapeutic success in low-level MRD patients suggests that the MRD-guided treatment strategy employed abrogated the unfavorable prognosis associated with slow clearance of blast cells.9 In ALL, MRD-directed therapy also significantly improved outcome in low-level MRD patients; yet, they were defined as having 0.01% to 0.99% MRD.2 And (3) Loken et al reported that patients with a history of MRD, even if they converted to MRD-negativity, had poor outcome,2 which stands in strong contrast to what was seen in AML if MRD was acted on,3 or in ALL.1

Buccisano et al discussed whether in AML a higher level of MRD at which a significant influence on disease outcome is found may result from less-intensive initial induction therapy, based on an observed lower prognostic MRD level of ~ 0.035% when they intensified induction.10 Yet intensifying induction with elevated cytarabine failed to change the incidence of MRD or affect outcome,9 possibly because of the ineffectiveness of this drug against leukemic stem cells, which contribute to the negative impact of MRD in AML.5 In the trial by Loken et al, the composition of their MRD antibody panel did not allow the detection of leukemic stem cells as part of MRD,2 an unfortunate drawback of many MRD studies. The multifaceted face of MRD is further highlighted by the impact of presenting genetic features on MRD levels during treatment both in ALL1 and AML.2 Nevertheless, evidence from the St Jude trials suggests that with the improved transplant procedures of today, the impact of MRD levels on survival remained significant only for ALL7,9 but not for AML,8 supporting a true biologic difference with respect to MRD between these two diseases.

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The SPMs included acute leukemias as well as solid tumors. In each of these trials, the risk of SPMs (excluding nonmelanoma skin cancers) was 2% to 3% in the placebo group versus 7% to 8% in the lenalidomide group. These differences were statistically and clinically significant and stunned most myeloma researchers because lenalidomide was considered one of the safest antimyeloma drugs, with an excellent overall side-effect profile. Since the initial reports surfaced there has been a virtual explosion of studies reporting on the risk of SPMs in multiple myeloma and the precursor premalignant stage of monoclonal gammopathy of undetermined significance.

Here, Usmani and colleagues provide additional information on the risk of SPMs associated with prolonged therapy with lenalidomide and thalidomide. Of note, one of the trials they investigated, Total Therapy 2 (TT2), represents the only other randomized trial (aside from the 3 lenalidomide maintenance trials) with prolonged drug exposure and an appropriate control arm that could be used to interrogate the association of immunomodulatory agents and melphalan with SPMs. Their study shows a trend to increased risk of solid SPMs in the thalidomide arm of TT2 compared with the control arm, although the difference did not achieve statistical significance. No increase was noted in the risk of hematologic SPMs with thalidomide therapy. The authors also report an overall rate of SPMs in the total therapy trials that approached the rate seen in the lenalidomide maintenance trials. The lack of a control arm and shorter duration of follow-up make this study less suitable to examine the association of lenalidomide with SPMs.

How should we interpret the plethora of information on SPMs in myeloma? First, although the various studies of SPMs in myeloma that have ensued in the wake of the lenalidomide maintenance trials are of considerable importance, it is important to recognize their place in the big picture, and not allow the vast amount of information to create a smokescreen. Just as randomized, placebo-controlled trials are the gold standard to determine treatment efficacy, they are just as powerful and credible in determining the specific risks associated with therapy. Thus, no amount of uncontrolled observational studies can mitigate or negate the association between lenalidomide and SPMs seen in 3 randomized trials. The appropriate control population to compare the risk of SPMs is the placebo arm of these trials, not the Surveillance, Epidemiology, and End Results (SEER) registry or rates seen in other trials. Second, although the risk of SPMs with lenalidomide appears to be real, such risks have only been seen in the context of melphalan exposure and in the setting of prolonged maintenance therapy. So far, no increase in risk has been reported from studies that used lenalidomide without accompanying melphalan exposure, or in studies in which the median duration of therapy was short, as in the case of relapsed refractory myeloma. This suggests that an initial strategy to counter the risk would be to simply limit exposure to concurrent melphalan as much as possible, and to limit the duration of lenalidomide maintenance (if employed) to 2 years. Third, as always, there is a need to balance risks and benefits. For the approved indication of lenalidomide in patients with relapsed myeloma, the benefits clearly outweigh the risks. Similarly, in frontline therapy without concurrent melphalan, regimens such as lenalidomide plus dexamethasone remain safe and effective options. In contrast, more care is needed for the use of lenalidomide in the maintenance setting where there is antecedent high-dose melphalan exposure coupled with the prospect of prolonged use. Here more data are needed on the type of patients most likely to benefit from maintenance, as well as the optimal duration of therapy. Finally, the study by Usmani and colleagues suggests that the risk of SPMs, at least solid tumors, may be an issue with thalidomide as well. It is hard to determine whether the risk is different in magnitude compared with lenalidomide because the comparisons are not randomized. Further, the number and variety of drugs used in the Total Therapy trials makes it harder to isolate the effect of individual drugs on SPMs. Although it is tempting to be reassured by the statistically insignificant \( P \) values, the slope of the incidence curves is a call to caution and the need for more follow-up.

Given the remarkable progress made in myeloma therapy in the past decade, therapy-induced SPMs represent a small but serious bump in the road. Identification of the biologic mechanisms involved, associated risk factors, and strategies for prevention will be of critical importance. SPMs are serious cancers that may be a necessary consequence of life-saving treatment in myeloma, but in terms of importance and the need to eliminate as much as possible, they are second to none.

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Comment on Weng et al, page 1613

Toward an off-the-shelf vaccine for B-cell malignancies

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While idiotype vaccines have shown promise for B-cell malignancies, production is cumbersome; thus, targeting a common antigen on malignant B cells using an off-the-shelf approach would provide significant logistical advantages.

Bendandi et al demonstrated early on that complete molecular remission in lymphoma patients who had received a patient-specific idiotype vaccine is possible.1 In a follow-up randomized phase 3 study, Schuster et al showed that vaccination with a patient-specific anti-idiotype vaccine led to improved disease-free survival in patients with follicular lymphoma.2 Patients enrolled in study who achieved a complete response to chemotherapy were randomly assigned to vaccine with idiotype conjugated to keyhole limpet hemocyanin (KLH) with local GM-CSF versus KLH control. The median disease-free survival for vaccine-treated patients was 44.2 months versus 30.6 months for patients in the control arm (hazard ratio 0.62; P = .047). However, this patient-specific vaccine required a significant amount of time to produce (6-12 months was allowed). Only 69% of patients randomized remained in complete response to chemotherapy by the time vaccine was available, making the remaining 31% ultimately ineligible to receive vaccine or placebo. Nevertheless, the promising disease-free survival seen among vaccinated patients provides hope that therapeutic vaccines will prove to be a well-tolerated treatment associated with clinical benefit in the setting of minimal disease.

The complexity of making a patient-specific vaccine can lead to significant financial and temporal costs (see figure). The only currently approved therapeutic vaccine for cancer is sipuleucel-T, which showed a statistically significant and clinically meaningful 22% reduction in risk of death in patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.3 The median 4.1-month improvement in survival was seen without significant side effects (only 1.5% of patients had to stop treatment because of toxicity). However, patients treated with sipuleucel-T must undergo apheresis at 3 time points and the vaccine is subsequently manufactured from the apheresis products at a central processing facility capable of rapid turnaround. This complexity adds to the price of the vaccine: $93 000 US for a complete course of treatment.4 Several off-the-shelf therapeutic vaccines have shown preliminary evidence of efficacy,5-7 providing hope that improvements in patient outcomes with this modality may lead to therapeutic options that are less resource-intensive.

Identification of a common antigen on B-cell malignancies that is not present on normal B cells thus offers the potential for an off-the-shelf vaccine for lymphomas that avoids the resource-intensive manufacture and release of patient-specific vaccines. In a convincing set of experiments described in this issue of Blood, Weng et al demonstrate that T-cell leukemia/lymphoma 1 (TCL1) oncprotein is overexpressed on a wide range of human B-cell lymphomas, but only selectively expressed on normal B cells.8 They demonstrate not only that TCL1 peptide-specific T cells could be generated from normal donors, but that TCL1-specific T cells were present in the blood of patients with lymphoma, and that these T cells could be expanded and, in an HLA-A2–restricted manner, could lyse autologous lymphoma cells but not normal B cells. This approach should help catalyze intensive translational efforts to rationally...
Second to none

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