Second to none

S. Vincent Rajkumar  MAYO CLINIC

In this issue of Blood, Usmani et al provide important information on second primary malignancies in patients treated with thalidomide and lenalidomide in the Arkansas total therapy trials.1

It took more than a decade for the association between melphalan exposure and acute myeloid leukemia to become apparent (see figure).2 It has taken about the same amount of time since the introduction of lenalidomide for something that warrants careful attention. Three recent randomized placebo-controlled trials have found a 2- to 3-fold increase in the risk of SPMs with the use of lenalidomide as maintenance therapy for patients with

CRITICAL FACTS

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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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REFERENCES
Comment on Weng et al, page 1613

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

James L. Gulley  NATIONAL CANCER INSTITUTE

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.

B endandi et al demonstrated early on that complete molecular remission in lymphoma patients who had received a patient-specific idiotype vaccine is possible. 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. 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. 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. Several off-the-shelf therapeutic vaccines have shown preliminary evidence of efficacy, 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) oncoprotein is overexpressed on a wide range of human B-cell lymphomas, but only selectively expressed on normal B cells. 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...
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