Targeting Agents Alone to Cure Acute Promyelocytic Leukemia
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Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) that is characterized by abnormal promyelocytes, a life-threatening bleeding syndrome, and t(15;17) chromosomal translocation. APL used to be the worst form of leukemia. The introduction of anthracycline-based chemotherapy in the 1970s yielded a complete remission rate of 70% and a long-term survival rate of 35 to 45%. The use of all-trans retinoic acid (ATRA) in the 1980s represented a revolution in APL treatment because of a high complete-remission rate (>90%) and an essential clue to the leukemogenicity of the chimeric gene product PML-RARA resulting from the t(15;17) translocation. APL was an early example of the application of effective therapies directed at a specific molecular abnormality. Indeed, the standard ATRA–chemotherapy combination allowed a 5-year event-free survival rate of over 70% in developed countries and about 50% in developing countries, including China.

In the 1970s, arsenic trioxide was already applied in the treatment of cancers, including APL in China, and a new strategy of APL therapy was developed in the 1990s. The ATRA–arsenic trioxide combination was complemented by chemotherapy for newly diagnosed APL, which led to a 5-year disease-free survival rate of 90%. Mechanistically, ATRA targets the retinoic acid receptor alpha (RARA) moiety of PML-RARA, whereas arsenic binds to the RBCC (RING finger, B boxes, and coiled-coil) domain of the PML moiety. The synergistic effects of ATRA–arsenic trioxide appear to result from degradation of PML-RARA and clearance of leukemia-initiating cells. These results raise a question: For patients with APL who have a relatively good prognosis, could the ATRA–arsenic trioxide combination be used alone as targeted therapy without chemotherapy?

Now, the answer has come thanks to a well-designed phase 3, multicenter, randomized clinical trial by Lo-Coco et al., published in this issue of the Journal. A total of 156 patients with newly diagnosed, low-to-intermediate-risk APL were analyzed. The efficacy and toxicity of the ATRA–arsenic trioxide combination for both remission-induction therapy and 28 weeks of consolidation therapy without chemotherapy were compared with those of the ATRA–chemotherapy protocol, comprising remission-induction therapy with ATRA–idarubicin followed by consolidation therapy with ATRA–chemotherapy and 2 years of maintenance therapy with low-dose chemotherapy and ATRA. The results were quite encouraging: complete remission was achieved in 77 of 77 patients in the ATRA–arsenic trioxide group who could be evaluated (100%) versus 75 of 79 patients in the ATRA–chemotherapy group (95%) (P = 0.12); with a median follow-up of 34.4 months, the 2-year event-free survival rates were 97% in the ATRA–arsenic trioxide group and 86% in the ATRA–chemotherapy group; the 2-year overall survival probability was 99% in the ATRA–arsenic trioxide group and 91% in the ATRA–chemotherapy group (P = 0.02).

The clinical observations together with sensitive detection of PML-RARA transcripts by means of reverse-transcriptase–polymerase-chain-reaction assay suggest that ATRA–arsenic trioxide may eradicate the leukemic clone in the vast majority of patients in the series reported by Lo-Coco et al. In addition, significantly fewer hematologic toxic effects and fewer infections were noted in the ATRA–arsenic trioxide group as compared with the ATRA–chemotherapy group. Although the hepatic toxic effects and prolongation of the corrected QT interval were more obvious in the ATRA–arsenic trioxide group, the hepatic toxic effects disappeared after temporary discontinuation of arsenic trioxide, ATRA, or both.

While the first eventual cure of APL by means of a synergistic targeted strategy without chemotherapy is heralded, there are still concerns to be addressed. First, the follow-up period is not long enough (median, 34.4 months), and data on survival rates much beyond 2 years are not available. Although this is generally an adequate follow-up period in patients treated with chemotherapy, in whom relapses tend to occur mostly in the first 2 years after treatment, it could be too early to evaluate the omission of maintenance therapy in the ATRA–arsenic trioxide group. To this end, the trial design might be even better if the ATRA–arsenic trioxide group
could undergo further randomization into two groups, one with maintenance treatment and the other without it.

Second, the current risk-stratification system for APL (low, medium, and high risk) is based only on white-cell count and platelet count. With the discovery of new genetic biomarkers, the few patients with APL who have an inferior prognosis among the clinically apparent low-to-intermediate-risk group, such as the two patients in the ATRA–arsenic trioxide group who had a relapse in this study, could eventually be predicted. This was the case in a previous report in which one of four patients who had a relapse after ATRA–arsenic trioxide–chemotherapy treatment carried, in addition to PML-RARA, a DNMT3A mutation, which is now considered to be a marker of a poor prognosis.

Third, for those high-risk patients, new trials of more sophisticated therapy are warranted. Early death before the therapeutic agents take effect, often encountered in this group, should be handled with the use of a multidisciplinary approach. For example, chemotherapy and other agents targeting additional genetic defects in malignant cells should be more appropriately incorporated into an ATRA–arsenic trioxide regimen in order to get closer to our goal of curing all patients with APL.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Combination Checkpoint Blockade — Taking Melanoma Immunotherapy to the Next Level

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Wolchok et al. and Hamid et al. report in the *Journal* the results of phase 1 clinical trials showing that the combination of PD-1 and CTLA-4 antibody blockers leads to improved treatment outcomes in patients with melanoma, without an escalation of toxic effects. The results of these trials are striking and complementary. In the trial by Hamid et al., a PD-1 monoclonal antibody was administered in patients who had had a relapse after CTLA-4 antibody monotherapy (ipilimumab); the authors found that durable and clinically significant responses were as common and robust as were those observed in patients who had not received ipilimumab therapy previously. Thus, progression of melanoma after anti–CTLA-4 therapy does not preclude a response to anti–PD-1 therapy. Wolchok et al., who in part report similar data for sequential CTLA-4 and PD-1 antibody therapy, also tested concomitant administration and found that at the maximum tolerated dose, 53% of patients with advanced, treatment-resistant melanoma had objective tumor responses, with tumor regression of at least 80% in every patient who had a response. Surprisingly and importantly, the use of ipilimumab and either one of two PD-1 mono-