remain unanswered. First, the optimal number of consolidation cycles with As$_2$O$_3$-containing frontline therapy has not been addressed adequately. Investigators at the MD Anderson Cancer Center incorporated 4 consolidation cycles into their frontline regimen consisting of ATRA plus As$_2$O$_3$ with or without gemtuzumab. Iland et al in this article used a very similar regimen, but included only 2 cycles of consolidation and added idarubicin during induction. Despite the considerably shorter consolidation compared with other studies, Iland and colleagues observed the remarkable outcome, which is a testament to the potency of ATRA and As$_2$O$_3$ combination and suggests that shorter consolidation may be sufficient when idarubicin is added during induction. Second, the optimal schedule of intravenous As$_2$O$_3$ during consolidation is unknown. Continuous, 6 d/wk and 5 d/wk schedules have all been used, but have never been compared with one another. The dose-dependent As$_2$O$_3$-associated toxicity noted by Iland et al favors the 5 d/wk schedule, which may be particularly suitable for older patients. Third, the role of maintenance with the As$_2$O$_3$-based therapy remains controversial. All of the patients in this study achieved molecular CR after consolidation. Given recent studies suggesting that maintenance may not be required for patients in molecular CR after standard ATRA plus anthracycline-based chemotherapy, future trials of As$_2$O$_3$-based frontline therapy need to carefully examine the role of maintenance. Lastly, it is unclear whether additional cytotoxic agents are required for non–high-risk patients treated with ATRA plus As$_2$O$_3$-based therapy. The MD Anderson study reported that non–high-risk patients without hyperleukocytosis during induction remained free of relapse without any chemotherapy exposure. Iland et al used idarubicin in all patients regardless of the presenting WBC counts, and it is difficult to glean from the study whether idarubicin is responsible for the excellent outcome or can be safely omitted in non–high-risk patients. Future trials incorporating risk-adapted anthracycline administration during induction will hopefully be able to answer this question.

The work by Iland et al highlights the remarkable ability of the ATRA and As$_2$O$_3$ combination to treat APL with minimal anthracyclines, and paves the way to cure the disease only with the rationally combined targeted agents. However, the challenge remains to define appropriate chemotherapy exposure during induction, determine the role of oral As$_2$O$_3$, evaluate the optimal number of consolidation cycles, and examine the requirement for maintenance with As$_2$O$_3$-based frontline therapy.

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Comment on Loken et al, page 1581

When it comes to MRD, AML ≠ ALL

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In this issue of Blood, an AML trial by Loken and colleagues from the Children’s Oncology Group (COG) retrospectively demonstrates clinical significance of MRD. These data reaffirm that AML–MRD is unlike ALL–MRD.

Despite overall optimism that MRD will help shape future risk-allocation algorithms, prospective trials in which treatment interventions are based on MRD levels in AML have been rare and with few, yet unpublished exceptions, limited to pediatric disease. Confidence in MRD as an efficacy biomarker has prompted the US Food and Drug Administration to hold a recent workshop on MRD as surrogate end point, occurring before standard end points, in the context of the evaluation and accelerated approval of novel drugs in ALL.

Disappointingly, in AML, we are far away from understanding the full potential of MRD to assess the quality of a patient’s response to a given therapy and to predict outcome. This has hampered the introduction of MRD into prospective AML trials. The article by Loken et al provides an opportunity to discuss pressing issues with respect to MRD; first, whether evidence from retrospective analyses can translate into prospective MRD-driven clinical trials, and second, how MRD in AML compares with the experience in ALL.

Loken was among the first to suggest that immunophenotypic patterns of AML blast cells are sufficiently at variance with the antigenic patterns expressed by normal bone marrow cells during maturation to allow them to be recognized when present at exceedingly low levels. This “different-from-normal approach,” also used in this study, contrasts with the more common concept of leukemia-associated immunophenotypes (LAIPs), in that it identifies AML cells as clusters clearly separated from the corresponding normal...
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.4 These cut-off levels for prognostic MRD in AML,1-8 versus AML,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 AML9 and ALL7 trials and the retrospective AML data by Loken et al?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, AML 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) 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.7 And (3) Loken et al reported that patients with a history of MRD, even if they converted to MRD-negativity, had poor outcome,6 which stands in strong contrast to what was seen in AML if MRD was acted on, 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 ALL7 and AML. The multifaceted face of MRD is further highlighted by the impact of presenting genetic features on MRD levels during treatment both in ALL7 and AML. 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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