interact with the N- or C-terminal region of SCL, and thus, it is speculated that ΔbHLH SCL functions against WT SCL through the competition for binding to these proteins. To further explore the underlying biochemical mechanisms, we have sequenced some of these coprecipitated proteins, which we hope will be reported in the near future.

To the editor:

Potential curability of newly diagnosed acute promyelocytic leukemia without use of chemotherapy: the example of liposomal all-trans retinoic acid

Several years ago we reported that liposomal all-trans retinoic acid (L-ATRA) used alone might cure some patients with untreated acute promyelocytic leukemia (APL). The median follow-up was 1.5 years from complete remission (CR) date. Because the risk of relapse does not decrease appreciably until considerably later, we herein update the study. The L-ATRA dose was 90 mg/m² every other day until CR, after which this dose was given 3 times weekly for 9 months. Using a sensitivity level of 10 (−4), polymerase chain reaction (PCR) testing for the promyelocytic leukemia/retinoic acid receptor[alpha] (PML-RAR) (fusion protein) was done every 3 months for 2 years from CR date. If positive, the test was repeated 2 to 4 weeks later. If again positive (“molecular relapse”), patients received 12 mg/m² idarubicin 3 times daily every 4 to 5 weeks for 3 courses. Thirty-four patients, median age 49 years, median white blood cell count (WBC) 2000/µL, were treated: 8 had high risk (WBC count > 10 000/µL) using Sanz et al’s system. The CR rate was 26 of 34, but only 3 of 8 in high-risk patients. Of the 34 patients, 10 (29%, 95% CI 15%-47%) remain alive in first CR at a median of 4.5 years (range, 3-0-5.5 years) from CR date despite never receiving other anti-APL therapy. In each case, the most recent PCR test is negative, having been obtained a median of 3.2 years (range, 1.4-5.5 years) from CR date. The remaining 16 patients who entered CR received idarubicin; in one of these, the reports of the relevant PCRs were later changed to negative and in another only a single PCR test was positive.

Thus, 14 patients “required” idarubicin: 8 had molecular relapse (at a median of 9 months from CR date), 2 failed to achieve molecular CR despite 6 months of L-ATRA monotherapy, and 4 had simultaneous clinical and molecular relapse (at a median of 17 months from CR date). The 10 patients who never received treatment other than L-ATRA each had a presenting WBC count less than 10 000/µL, as did 13 of the 14 who required idarubicin. The 2 groups also had similar distributions of initial WBC count, platelet count, and type of PML-RAR (isoform and age). The PCR status at CR was of no discriminatory value since all patients but one were PCR positive at CR, with 24 of 26 becoming negative by 3 months. Of the 10 patients whose first indication of failure was molecular, 9 received idarubicin in (hematologic) CR. Of those, 6 remain in hematologic CR, while 3 had hematologic relapse, which occurred within 1 year of molecular failure.

The immediate significance of our results is limited. L-ATRA is unavailable commercially. The 3 of 8 CR rate in high-risk patients seems extraordinarily low. Furthermore, while possibly sparing two fifths (ie, 10 of 26) of low-risk patients the need for chemotherapy, L-ATRA was not free of toxicity and required 3 intravenous infusions weekly. Nonetheless, the observation that patients can be potentially cured of APL without use of chemotherapy should encourage further attempts in the same direction as, for example, in our current trial using ATRA and arsenic trioxide.

We disagree with the comment by the questioners that we should be able to show the rescue of the effect of ΔbHLH SCL with WT SCL. This is not an appropriate experiment to show the dominant-negative effect of ΔbHLH SCL.

Although the biochemical mechanisms need to be further disclosed, clear are our findings on the distinct biologic functions of WT SCL and ΔbHLH SCL on the commitment fate determination of hematopoietic stem cells. We hope that our ongoing study will give a clear answer to the mechanisms for how ΔbHLH SCL functions in a dominant-negative fashion against WT SCL.

Atsushi Kunisato, Seishi Ogawa, and Shigeru Chiba

Correspondence: Shigeru Chiba, Department of Cell Therapy and Transplantation Medicine, University of Tokyo Hospital 7-3-1, Hongo, Bunkyo-ku, Tokyo; e-mail: schiba-tky@umin.ac.jp.

References

Figure 1. Proteins co-precipitated with WT SCL or ΔbHLH SCL. WT SCL and ΔbHLH SCL are indicated by asterisks. The bands indicated by arrows are reproducibly precipitated.
Reproducible measurements of AML blast p-glycoprotein function in 2 center analyses

The review article “Targeting the Multidrug Resistance-1 Transporter in AML” by Mahadevan and List is thorough and thought-provoking, and we support its principal conclusions that p-glycoprotein (pgp) remains one of the most powerful prognostic factors in adult acute myeloid leukemia (AML) and that future trials of pgp modulators are called for. Since the preselection of patients with pgp-positive AML would target those who are most likely to benefit and would also improve the predictive power of modulator trials, it follows that pgp phenotyping should be carried out at diagnosis. However, Mahadevan and List were unable to indicate a suitable method for pgp measurement in the laboratory. They referred right back to the consensus recommendations of 1996 and to the French report of 1997, both of which highlighted discrepancies in methodology and analysis. Meanwhile, Broxterman and colleagues published a report of a flow cytometric assay of functional pgp, which was reproducible in 2 centers in The Netherlands. In the United Kingdom, where pgp is being measured on AML trial patients in more than one laboratory, we built on the lessons of the Dutch and the French groups and decided to use a single standard operating procedure at participating laboratories. The Dutch protocol was adopted with the minor modification of adding CD45 staining to identify blasts.

Most samples were sent to one of 2 centers, Cardiff or Nottingham. Thirteen quality control samples have been shared between the 2 centers since our collaboration started in 1999. Discordant results were noted in 1 of 13 samples; 8 had negative or low values (less than 1.7), 2 had intermediate values (1.7-3.39), and 2 had high values (3.4). Furthermore, there was a remarkable similarity in the distributions of data. Figure 1 illustrates the distributions obtained on 120 samples, the first 60 analyzed at each center. At one stage in the trial a third center also participated in the functional pgp analysis. A Kolmogorov-Smirnoff test showed no significant difference in the distribution of PSC-833 modulation ratios at each of the 3 centers.

In contrast to the functional assays, antibody assays using MRK-16, also performed according to a standard operating procedure, showed significant differences in distribution between the 3 centers. While Mahadevan and List rightly pointed out that functional assays do not yield greater prognostic significance than antibody measurement in clinical trials, we have found that an important advantage of the functional assay lies in its greater sensitivity and reproducibility. We acknowledge that discrepancies do occur between phenotypic and functional pgp results, which are not fully understood. However, in the United Kingdom LRF AML 14 trial, an additional advantage of using a pgp functional assay was that the agent being used in the trial, PSC-833, could also be used in the assay.

Using the Dutch protocol over several years has confirmed to us that this methodology is robust and could now be passed to the safe and reliable hands of hospital immunophenotyping laboratories. From receiving a narrow sample, the assay takes about 4 hours and has been undertaken with as few as 3 x 10^6 cells. Using this protocol, future trial organizers can have the choice of whether to give pgp modulators to an unsorted cohort or to pgp-positive patients only.

Monica Pallis, Janet Fisher, Louise Truran, Martin Grundy, Nigel Russell, and Alan Burnett

Correspondence: Monica Pallis, Academic Haematology, Clinical Sciences Building, Nottingham City Hospital, Nottingham NG5 1PB, UK; e-mail: monica.pallis@nottingham.ac.uk

These studies were funded by the Leukaemia Research Fund. We acknowledge the support of the NCRN Leukaemia Working Party.

References

6. Pallis M, Das-Gupta E. The flow cytometric measurement of functional and
Potential curability of newly diagnosed acute promyelocytic leukemia without use of chemotherapy: the example of liposomal all-trans retinoic acid

Elihu Estey, Charles Koller, Apostolia M. Tsimberidou, Susan O'Brien, Miloslav Beran, Jorge Cortes, Maribel Tirado-Gomez, Gabriel Lopez-Berestein and Hagop Kantarjian

Updated information and services can be found at:
http://www.bloodjournal.org/content/105/3/1366.full.html

Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml