CORRESPONDENCE

COMPLETE REMISSION AFTER FLUDARABINE FOR CHRONIC LYMPHOCYTIC LEUKEMIA

To the Editor:

We would like to make a contribution to the report from Robertson et al[1] of the MD Anderson Cancer Center of results they achieved by treating patients suffering from chronic lymphocytic leukemia (CLL) with a combination of fludarabine and prednisolone. Reviewing their experience with 161 patients, they documented 19 complete remissions (CRs) by standard morphologic assessment[2] of bone marrow aspirates and biopsies. They further demonstrated that 17 of these 19 patients had no detectable residual disease by two-parameter flow cytometry and that in a subgroup of 9 of these patients in whom molecular studies were performed before and after treatment, clonal Ig gene rearrangement could no longer be detected by Southern blotting in 7 patients.

We have treated 14 patients with CLL using fludarabine at a dose schedule of 25 mg/m^2 intravenously daily for 5 days repeated every 4 weeks to a maximum of six courses; no patients received concurrent steroids. We have also attempted to pursue the assessment of minimal residual disease in our patient population and identified three patients who achieved CR by morphologic criteria; none of these patients showed persistence of residual lymphoid marrow nodules in the trephine biopsy. We also monitored our patients for response by immunophenotyping and DNA electrophoresis by Southern blotting using the Ig heavy chain probe JH. Additionally, we undertook DNA amplification by polymerase chain reaction (PCR) analysis using a semi-nested method with concensus primers to amplify the CDR III region of the immunoglobin heavy chain gene.[3] Immunophenotyping at diagnosis (by flow cytometry on a Becton Dickinson FACScan [Becton Dickinson, Mountain View, CA]) included single reagent staining with fluorescein isothiocyanate (FITC)-conjugated monoclonal antibodies to several antigens (CD2, CD3, CD5, CD19, CD4, CD8, and HLA-DR) and dual-color staining with phycoerythrin (PE)-conjugated anti-CD19/FITC–conjugated CD5, PE-conjugated anti-CD19/FITC–conjugated anti-κ or anti-λ (all reagents from Dako, Glostrup, Denmark). Samples of bone marrow after treatment were assessed for the presence of monotypic light chain expression (defined as a threefold light chain excess) and for the presence of any CD5/CD19 double-stained cells. Using bone marrow lymphocytes separated using density fractionation, internal (dilutional) controls indicate the following levels of sensitivity for these techniques: dual-color immunophenotype, 1 in 10^2 cells; Southern blotting, 1 in 10^2 cells; semi-nested PCR, 1 in 10^4 cells.

The characteristics of our three CR patients are shown in Table 1. None of these patients has yet shown evidence of clinical recurrence of CLL and two remain without any detectable residual disease by any method. Notably, DNA electrophoresis after PCR amplification shows only a broad smear, indicative of the presence of polyclonal B cells.

We agree with the conclusions of Robertson et al[1] that CR is now obtainable in patients with CLL treated with fludarabine and that the sensitivity of techniques used to detect minimal residual disease may now be used to predict the duration of remission.

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STEPHEN A. JOHNSON
DEBORAH RICHARDSON
JOHN HOPKINS
DENISE HOWE
MALCOLM J. PHILLIPS
Department of Haematology
Taunton and Somerset Hospital
Musgrove Park, Taunton
Somerset, UK

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Table 1. CR Patient Characteristics

Patient No.	Age/Sex	Pretreatment: Prior Therapy	Pretreatment: PBL (×10^9/L)	Pretreatment: BM Pattern	Pretreatment: Rai Stage	Posttreatment: Residual Flow	Posttreatment: Residual DNA: Southern	Posttreatment: Residual DNA: PCR	Posttreatment: Follow-up: Flow	Posttreatment: Follow-up: PCR	Posttreatment: Follow-up: Weeks
1	58/M	Yes	57.0	Nodular	II	No	No	No	No	Yes	88
2	59/M	No	18.1	Mixed	II	No	No	No	No	No	72
3	53/M	Yes	45.8	Nodular	II	No	No	No	No	No	100

Abbreviations: PBL, peripheral blood lymphocytes; BM, bone marrow.