CORRESPONDENCE

To the Editor:

The paper by Koeffler et al1 on the effects of 13-cis-retinoic acid (13CRA) vs placebo in myelodysplasia (MDS) raises several interesting points. There is little conflict between their data and those in our report presented last year.2 We found no clinical improvement or lengthening of survival in patients with refractory anemia or lengthening of blast cells (RAEB) or those with sideroblastic anemia treated with 13CRA,2 and these constituted over half of the patients in the study of Koeffler et al. We found little toxicity at a daily dose of some 20 mg 13CRA, while a substantial proportion of patients treated with Koeffler et al with high doses of the drug stopped treatment and we do not know how complete compliance was in the remainder. The positive result in our study was that at a 13CRA dose of 20 mg daily, patients with refractory anemia had a 1-year survival rate of 77% as compared with 36% in the control group.2,3 These results clearly require confirmation by a larger study.

When considering MDS either in terms of clinical state or response to therapy, it is no longer satisfactory to amalgamate all patients into a single group and expect them to behave in a uniform manner. The different behavior of the various French-American-British subtypes has been well demonstrated, and we have suggested

50% inhibition (IC_{50}) of 85 μg/mL (Fig 1). In addition, irreversible irregularities in contractions of the atrial trabeculae were noted in 40% of all preparations at doses of 60 μg/mL. DEHP, as well as albumin or bicarbonate alone, had no significant effect on the contractile characteristics of the trabeculae.

To determine the relative exposure of cardiac surgical patients to MEHP, we then examined blood levels of the plasticizers before and after surgery. These patients received plasticizer both through the use of stored blood and blood components and through the extracorporeal circuitry used in the CPB procedures. Samples of whole blood were taken from the Swan-Ganz catheter inserted into patients undergoing coronary artery bypass graft surgery (CABG), orthotopic transplantation, Jarvik 7-70 total artificial heart implantation during bridge-to-transplant, and corrective surgery for congenital defects. By the end of CPB, the DEHP and MEHP blood levels rose approximately tenfold above those measured prior to CPB, with infants having the highest circulating levels (2.7 μg/mL MEHP and 5.1 μg/mL DEHP). In most patients, DEHP and MEHP returned to preoperative levels within 24 hours, but in patients whose urinary output was low, both compounds were still detectable 120 hours postoperatively.

The patient data demonstrated that the concentration of MEHP causing a 50% decrease in developed force in the isolated atrial preparation was only 20- to 30-fold higher than the circulating levels measured in patients on CPB. Since the target organ for the significant toxic effect of MEHP is the heart, which is already compromised in patients undergoing CPB, we suggest that exposure to MEHP might be another risk that should be considered in infants and in adult patients with multisystem failure, in whom the highest circulating levels of MEHP were measured.

YVONNE A. BARRY

ROSALIND S. LABOW

GAIL ROCK

Ottawa Center

Canadian Red Cross

Blood Transfusion Service

Ottawa, Canada

WILBERT J. KEON

Department of Surgery

University of Ottawa Heart Institute

Ottawa, Canada

REFERENCES


Fig 1. Effects of MEHP on isometric contractile force (DF) in electrically driven human right atrial trabeculae. Data are derived from atria maintained in a Krebs-Henseleit bicarbonate buffer solution at 34°C and stimulated at 1 Hz. A total of 36 trabeculae were harvested from human right atrial appendages from 22 patients who underwent CABG (n = 18), mitral valve replacement (n = 3), and aortic valve replacement (n = 3). There were no significant differences among the trabeculae used for the control (n = 18) and experimental groups (n = 18) with respect to weight, length, cross-sectional area, resting or developed force. (A) Control trabeculae. NaHCO_3 alone; (△) MEHP dissolved in NaHCO_3.

13-cis-RETINOIC ACID v PLACEBO IN MYELODYSPLASIA

To the Editor:

The paper by Koeffler et al1 on the effects of 13-cis-retinoic acid (13CRA) vs placebo in myelodysplasia (MDS) raises several interesting points. There is little conflict between their data and those in our report presented last year.2 We found no clinical improvement or lengthening of survival in patients with refractory anemia or lengthening of blast cells (RAEB) or those with sideroblastic anemia treated with 13CRA,2 and these constituted over half of the patients in the study of Koeffler et al. We found little toxicity at a daily dose of some 20 mg 13CRA, while a substantial proportion of patients treated with Koeffler et al with high doses of the drug stopped treatment and we do not know how complete compliance was in the remainder. The positive result in our study was that at a 13CRA dose of 20 mg daily, patients with refractory anemia had a 1-year survival rate of 77% as compared with 36% in the control group.2,3 These results clearly require confirmation by a larger study.

When considering MDS either in terms of clinical state or response to therapy, it is no longer satisfactory to amalgamate all patients into a single group and expect them to behave in a uniform manner. The different behavior of the various French-American-British subtypes has been well demonstrated, and we have suggested...
survival in our control group as compared with cases from other used in the Cardiff series, including a strict interpretation of threefold difference in median survival seen in various series. The sometimes be effective at one stage of the disease but not at others. Criteria for the diagnosis of refractory anemia may be interpreted differently in different centers, and indeed it has been suggested that they may sometimes be difficult to interpret at all. This is reflected by the threefold difference in median survival seen in various series. The criteria used in the Cardiff series, including a strict interpretation of blast cells, tend to include cases of somewhat greater malignancy than do many other series, and this accounts for the lower median survival in our control group as compared with cases from other centers.

Despite the difficulties in standardizing diagnostic criteria, we would like to suggest that therapeutic trials in patients with MDS take care, as far as possible, to consider responses in relation to the stage of the disease. The inclusion in the same analysis of good-prognosis patients, such as those with sideroblastic anemia, together with refractory anemia and RAEB can only weaken the significance of the results.

ALLAN JACOBS
R.E. CLARK
Department of Haematology
University of Wales College of Medicine
Cardiff, Wales

REFERENCES

RESPONSE

To the Editor:

Our patients with the myelodysplastic syndrome were categorized into the five French-American-British subtypes; analysis of the response for each subtype of myelodysplasia showed no statistical difference when compared with the response of the placebo group.

REFERENCES

H. PHILLIP KOEFFLER
UCLA Department of Medicine
Division of Hematology/Oncology
Los Angeles

THE MURINE ERYTHROPOIETIN GENE IS LOCALIZED ON CHROMOSOME 5

To the Editor:

Erythropoietin (Epo) is a plasma glycoprotein hormone which controls RBC production through oxygen tension mechanisms. Both human and mouse Epo genes were recently cloned.

The human gene has been localized to the q21-22 region of chromosome 7. We report the mapping of the mouse Epo gene to the distal region of chromosome 5 by in situ hybridization and by genetic analysis, using restriction fragment length polymorphisms (RFLPs) in interspecific mouse backcross DNAs.

For these interspecific backcross analyses, C57Bl/6, BALB/c, WMP/Pas, SPE/Pas (Mus spretus) and the interspecific backcross progeny (C57Bl/6 × SPE) F1 × C57Bl/6 or (BALB/c × SPE) F1 × BALB/c, raised at the Institut Pasteur, Paris, were used.

Male backcross animals were also characterized by F. Bonhomme and colleagues (CNRS UA 327, Montpellier, France) for the segregation of 15 biochemical markers already localized on the mouse genetic map. High-mol-wt DNA was extracted from frozen spleen as previously described and was digested with appropriate restriction enzymes. Agarose gel electrophoresis, Southern blot transfers, and hybridizations were performed as described. The Epo probe used for the Southern blot analysis was a 1-kb Pst I restriction fragment of the mouse Epo gene, encompassing part of exons IV and V.

In situ hybridization experiments were performed using metaphase spreads from a male mouse of the WMP/Pas inbred strain, in which all autosomes except autosome 19 are involved in Robertsonian translocations. Concanavalin A-stimulated lymphocytes were cultured at 37°C for 72 hours; 5-bromodeoxyuridine was added for the final six hours of culture (60 μg/mL medium) to ensure a good quality chromosomal R-banding. The entire pUC 19 plasmid containing the 1-kb Epo fragment was titered by nick-translation to a specific activity of 1 × 106 dpm μg−1. The radiolabeled probe was then hybridized to metaphase spreads at a final concentration of 25 ng/mL hybridization solution, as previously described. After being coated with nuclear track emulsion (Kodak NTB2), the slides were exposed for 13 days at 4°C, then developed.
13-cis-retinoic acid v placebo in myelodysplasia [letter]

A Jacobs and RE Clark