Acute Lymphoblastic Leukemia

A randomized trial of dexamethasone before remission induction, in *de novo* childhood acute lymphoblastic leukemia

We evaluated the impact of adding dexamethasone before chemotherapy in 95 children with *de novo* standard-risk acute lymphoblastic leukemia (ALL). The children were randomly divided into 2 groups: one group was given dexamethasone, the other was not. The initial characteristics and mean follow-up of both groups were similar. Day +14 blast percentage was significantly lower in the dexamethasone group. Disease-free survival at 40-months follow-up was better (almost significantly so) in the dexamethasone group.

haematologica 2004; 89:365-366
(*http://www.haematologica.org/2004/3/365*)

The role of corticosteroids in the treatment of acute lymphoblastic leukemia (ALL) has long been established. Corticosteroids have been part of therapeutic regimens for ALL since treatment of this disease started, and recently dexamethasone has appeared to be better than prednisone at achieving event-free survival when used during remission induction.[1,2] Various authors have addressed the possible predictive value of steroid response, for treatment outcome in children with ALL.[3,4] It has been demonstrated that steroid treatment is effective in inducing immediate blast cell apoptosis.[5] It has also been suggested that rapid leukemic cell-killing in patients with ALL could promote a favorable outcome.[6] However, the advantage of dexamethasone use prior to remission induction remains to be validated.

The aim of our study was to evaluate the impact of giving dexamethasone four days before starting chemotherapy on bone marrow blast percentage at day +14, on remission rate and on disease-free survival, in standard-risk *de novo* ALL patients up to 20 years old.

Between 1996 and 2000, a total of 95 consecutive eligible patients with *de novo* ALL from a single institution entered the study and were randomized to one of the groups. The study was approved by our institution's review board and informed consent was obtained from the patients' parents or guardians. Patients had no other organ failures, and were in the standard risk category according to the Cancer Therapy Evaluation Program.[7]

The patients were randomized to receive IV dexamethasone 10 mg/m^2/day on days –4 to –1 before chemotherapy (DEX arm) or to start receiving the Memorial Sloan-Kettering-New York-II protocol chemotherapy regimen immediately (NO-DEX arm).[8] Standard anti tumor-lysis syndrome prevention measures such as aggressive IV fluid administration, urine alkalinization and allopurinol were started 48 hours before the administration of dexamethasone in one group and before chemotherapy in the other.

Bone marrow aspirates were performed on the first day of chemotherapy for patients receiving dexamethasone, and on days +14 and +28 for all patients. Study endpoints were bone marrow blast percentage at day +14, remission induction, death, relapse rates, and disease-free survival (DFS), and included patients who died during treatment.

Fifty-two patients entered the DEX arm and 43 the NO-DEX arm. There were no statistically significant differences in mean age: 8.2 vs 7.7 years old (p=0.66), presence of mediastinal mass: 4 vs 1 (p=0.48), leukocyte count $\times 10^9$/L, 46 vs 56 (p=0.61), or B/T cell distribution 36/6 vs 27/6 (p=0.88) between the two groups. The female/male sex distribution was statistically different: 17/35 vs 26/17 (p=0.01). The median follow-up for both arms was 40 months. Karyotypic information was not available. Two patients younger than one year were included, one in each arm; the patient in the DEX arm is alive and disease-free at 16 months of follow-up; the patient in the NO-DEX arm relapsed and died 13 months after starting treatment. Causes of death in the DEX arm were: CNS bleeding (n=1), infection plus CNS bleeding (n=1), and infection (n=2). Causes of death in the NO-DEX arm were: infection (n=7), CNS bleeding (n=3), and pancreatitis (n=1). Relapse distribution (myeloid/CNS) in the DEX arm was 1/1 and in the NO-DEX arm 9/1.

The percentage of bone marrow blasts on day +14 was significantly different between the two arms. The difference in deaths during remission induction did not reach statistical significance (Table 1). Disease--free survival came close to being statistically significantly better in the DEX arm (p=0.07)(Figure 1).

Table 1. Results for both arms.

	DEX (n=52)	*NO-DEX (n=43)*	*p*
Day +14 blast percentage in the bone marrow, median (range)	3 (0-36)	9 (1-25)	0.004
Remissions, %	92.3	74.5	0.70
Deaths during induction, n	4	11	0.81
DFS at 40 months, %	92.5	70	0.076

DFS: disease-free survival.

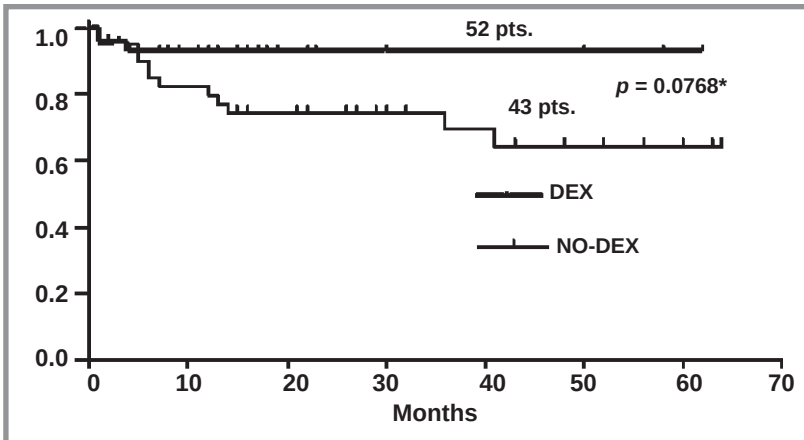

Figure 1. *95% confidence interval: 0.1331 to 1.109.

Cellular drug resistance is an important cause of failure of chemotherapy.[9] It has been reported that prior corticosteroid therapy could help identify a subset of Ph+ ALL patients who may be cured even if allogeneic bone marrow transplantation cannot be performed.[10]

Although our results showed no difference in remission induction rate or the number of deaths during remission therapy, the administration of IV dexamethasone for 4 days before starting chemotherapy did significantly decrease the bone marrow blast percentage at day +14, and the improved disease-free survival approached statistical significance. It is possible that dexamethasone increases the speed at which blasts are destroyed, but probably does not have any effect on blasts which are resistant to chemotherapy. Mid-term and long-term side effects, such as aseptic necrosis of the bone, will be assessed in a longer follow-up.

Our small number of patients precludes us from carrying out multivariate analysis, but we believe that, with more patients and a longer mean follow-up, this strategy will probably result in a significantly better disease-free survival than that achieved by the same chemotherapy regimen without prior administration of dexamethasone.

Manuel A. López-Hernández, Martha Alvarado,**
José De Diego, José R. Borbolla-Escoboza,°*
Rosa M. Jiménez, Elvira Trueba**

**From the Hematology Department, Centro Médico Nacional "20 de Noviembre", ISSSTE, Mexico city, Mexico;*
°Centro de Investigación de Ciencias de la Salud, School of Medicine, Instituto Tecnológico de Monterrey, Mexico

Key words: lymphoblastic leukemia, chemotherapy, corticosteroids, children.

Correspondence: José R. Borbolla, MD, Apartado 5091, sucursal Tecnológico, 64849, Monterrey, NL, México.
Phone/fax: international +52.81.83331121.
E-mail: borbolla@itesm.mx

References

1. Silverman LB, Gelber RD, Dalton VK, Asselin BL, Barr RD, Clavell LA, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. Blood 2001;97:1211-8.
2. Bostrom BC, Sensel MR, Sather HN, Gaynon PS, La MK, Johnston K, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. Children's Cancer Group. Blood 2003;101:3809-17.
3. Dordelmann M, Reiter A, Borkhardt A, Ludwig WD, Gotz N, Viehmann S, et al. Prednisone response is the strongest predictor of treatment outcome in infant acute lymphoblastic leukemia. Blood 1999;94;1209-17.
4. Ferster A, Benoit Y, Francotte N, Dresse MF, Uyttebroeck A, Plouvier E, et al. Treatment outcome in infant acute lymphoblastic leukemia. Blood 2000;95:2729-30.
5. Friesen C, Herr I, Krammer PH, Debatin KM. Involvement of the CD95(APO-1/Fas) receptor/ligand system in drug-induced apoptosis in leukemia cells. Nature Medicine 1996;2:574-7.
6. Uckan D, Yetgin S, Cetin M, Ozyurek E, Okur H, Aslan D, et al. The effects of high dose methylprednisolone on apoptosis in children with acute lymphoblastic leukemia. Clin Lab Haematol 2003; 25:35-40.
7. Smith M, Arthur D, Camitta B, Carroll AJ, Crist W, Gaynon P, et al. Uniform approach to risk classification and treatment assigned for children with acute lymphoblastic leukemia. J Clin Oncol 1996;14: 18-24.
8. Steinherz PG, Redner A, Steinherz L, Meyers P, Tan C, Heller G. Development of a new intensive therapy for acute lymphoblastic leukemia in children at increased risk of early relapse. The Memorial Sloan-Kettering-New York-II protocol. Cancer 1993;72:3120-30.
9. Schrappe M, Reiter A, Riehm H. Cytoreduction and prognosis in childhood acute lymphoblastic leukemia. J Clin Oncol 1996;14: 2403-6.
10. Schrappe M, Arico M, Harbott J, Biondi A, Zimmermann M, Conter V, et al. Philadelphia chromosome positive (Ph+) childhood acute lymphoblastic leukemia: good initial steroid response allows early prediction of a favorable treatment outcome. Blood 1998;92:2730-41.

Lymphoproliferative Disorders

Quantification of Epstein-Barr viral load and determination of a cut-off value to predict the risk of post-transplant lymphoproliferative disease in a renal transplant cohort

Post-transplant lymphoproliferative disorder (PTLD) is a life-threatening Epstein-Barr virus (EBV)-driven B-cell malignancy occurring in 1 to 3% of renal transplant patients.[1,2] Recently, EBV DNA quantification has become a useful tool for identifying patients at risk of developing PTLD.[3-5] However, studies on EBV load differ in design, methodology and type of patients.

haematologica 2004; 89:366-368
(*http://www.haematologica.org/2004/3/366*)

We conducted a nested case-control study[6] sampled in a cohort of 1,800 renal transplant recipients to estimate the threshold value of EBV load predictive of PTLD development. Eleven PTLD patients were enrolled between January 2000 and December 2002 from a single Institution. The diagnosis of PTLD was established according to the WHO classification[7] and confirmed by *in situ* hybridization for EBV, using an EBV-encoded RNA (EBER) detection kit (Dako, Glostrup, Denmark). Fifty-five controls (5 per case) matched by age, date of transplant, type and dosage of immunosuppression and history of rejection were selected from the cohort (Table 1). Using real-time polymerase chain reaction (PCR) (LightCycler System, Roche, USA)[8] and primers for the EBNA-1 gene of EBV,[9] we quantified the EBV load in whole blood of cases and controls (1 sample/individual). Each sample was analyzed in duplicate. Each run included two negative (no DNA) and two positive (DNA from Daudi EBV-positive cell line, ATCC CCI-213, Rockville, MD, USA) controls. Albumin RQ-PCR amplification was used as tthe internal control.[8] The sample quantification is based on a calibration curve, prepared with a known concentration of a purified PCR product (Daudi cell line). The DNA concentration of the PCR product is estimated by optical density at 260 nm, and the copy number/mL is calculated by the formula: copies/mL $=(6.023\times10^{23}\times C\times OD_{260})/$ MWt, where C= 5×10^{-5} g/mL and MWt is the molecular weight of the base pairs of the PCR product $\times$ 6.58 $\times$ 102g.[10] In order to validate EBV quantification, five comparative groups were used: 10 healthy blood donors, 10 individuals with AIDS (CD4 $\leq$ 100 cells/mm^3), 10 patients with untreated Hodgkin's lymphoma (HL), 10 individuals with infectious mononucleosis (IM) and 5 children aged from 6 to 18 months. All PTLD cases and controls presented positive EBV-IgG and negative IgM. All blood donors, all AIDS patients and 9 HL patients were IgG-positive (no signs of active infection). All children were EBV-negative and all IM patients displayed serological evidence of active infection. The median time from renal transplantation to PTLD onset was 36 months. All cases showed elevated EBV load at