Anthracycline dose intensification in AML

UWHC journal club
Feb. 19, 2010
Trevor Dennie, MD
Anthracycline Dose Intensification in Acute Myeloid Leukemia

Hugo F. Fernandez, M.D., Zhuoxin Sun, Ph.D., Xiaopan Yao, Ph.D., Mark R. Litzow, M.D., Selina M. Luger, M.D., Elisabeth M. Paietta, Ph.D., Janis Racevskis, Ph.D., Gordon W. Dewald, Ph.D., Rhett P. Ketterling, M.D., John M. Bennett, M.D., Jacob M. Rowe, M.D., Hillard M. Lazarus, M.D., and Martin S. Tallman, M.D.

ABSTRACT

BACKGROUND
In young adults with acute myeloid leukemia (AML), intensification of the anthracycline dose during induction therapy has improved the rate of complete remission but not of overall survival. We evaluated the use of cytarabine plus either standard-dose or high-dose daunorubicin as induction therapy, followed by intensive consolidation therapy, in inducing complete remission to improve overall survival.

METHODS
In this phase 3 randomized trial, we assigned 657 patients between the ages of 17 and 60 years who had untreated AML to receive three once-daily doses of daunorubicin at either the standard dose (45 mg per square meter of body-surface area) or a high dose (90 mg per square meter), combined with seven daily doses of cytarabine (100 mg per square meter) by continuous intravenous infusion. Patients who had a complete remission were offered either allogeneic hematopoietic stem-cell transplantation or high-dose cytarabine, with or without a single dose of the monoclonal antibody gemtuzumab ozogamicin, followed by autologous stem-cell transplantation. The primary end point was overall survival.

RESULTS
In the intention-to-treat analysis, high-dose daunorubicin, as compared with a standard dose of the drug, resulted in a higher rate of complete remission (70.6% vs. 57.3%; P<0.001) and improved overall survival (median, 25.7 vs. 15.7 months; P=0.003). The rates of serious adverse events were similar in the two groups. Median follow-up was 25.2 months.

CONCLUSIONS
In young adults with AML, intensifying induction therapy with a high daily dose of daunorubicin improved the rate of complete remission and the duration of overall survival, as compared with the standard dose. (ClinicalTrials.gov number, NCT00049517.)

From the Moffitt Cancer Center and Research Institute, Tampa, FL (H.F.F.); the Dana-Farber Cancer Institute, Boston (Z.S., X.Y.); the Mayo Clinic, Rochester, MN (M.R.L., G.W.D., R.P.K.); the University of Pennsylvania, Philadelphia (S.M.L.); the North Division of Montefiore Medical Center, Bronx, NY (E.M.P., J.R.); the University of Rochester, Rochester, NY (J.M.B.); the Rambam Medical Center, Haifa, Israel (J.M.F.); University Hospitals Case Medical Center, Cleveland (H.M.L.); and Northwestern University Feinberg School of Medicine, Chicago (M.S.T.). Address reprint requests to Dr. Fernandez at the Department of Blood and Marrow Transplantation, Moffitt Cancer Center and Research Institute, University of South Florida, 12902 Magnolia Dr., Rm. 3116, Tampa, FL 33612, or at hugo.fernandez@moffitt.org.

Findings in NEJM study 9/24/09 (Fernandez et al, younger pts)

► Eligible pts 17-60 yrs old with untreated AML
► Randomized to 7+3 induction at std. dose (45 mg/m2) or higher-dose (90 mg/m2) daunorubicin
► Pts w/ CR from both arms eligible for allogeneic SCT or consolidation chemo + auto transplant
► Primary end point: OS
► Results favor higher-dose arm:
  ▪ CR 70% vs 57%
  ▪ OS 23.7 vs 15.7 mos.
  ▪ Similar AE profile