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612. ACUTE LYMPHOBLASTIC LEUKEMIA: CLINICAL STUDIES:
ADVANCES IN THE TREATMENT OF ALL | DECEMBER 07, 2017

CA180-372: An International Collaborative Phase 2 Trial of Dasatinib and Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

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Abstract

Introduction: Ph^+ ALL comprises ~5% of childhood and adolescent ALL. Prior to development of tyrosine kinase inhibitor (TKI) therapy, survival rates were poor. Less than half of patients (pts) survived despite treatment with intensive chemotherapy and frequent use of allogeneic hematopoietic stem cell transplant (HSCT) in first remission (CR1). The Children's Oncology Group (COG) AALL0031 trial (Schultz, *JCO* 2009) and the EsPhALL trial (Biondi, *Lancet Oncology* 2012) showed adding imatinib to different intensive chemotherapy backbones improved event-free (EFS) and overall survival (OS) in pediatric Ph^+ ALL. Dasatinib is attractive to study in Ph^+ ALL because it is a dual ABL/SRC TKI that is 300 times more potent than imatinib *in vitro*, is active against most ABL1 TKI domain mutations that cause imatinib resistance, and accumulates in the central nervous system (CNS), a sanctuary site for ALL where imatinib penetration is poor.

Methods: We conducted a phase 2 trial of dasatinib added to the EsPhALL chemotherapy backbone in pediatric (>1-17.99 years (yrs) of age) Ph^+ ALL pts at COG sites in North America and Australia and EsPhALL sites in Italy and the United Kingdom. Protocol therapy added continuous daily dasatinib (60 mg/m^2) at day 15 of induction chemotherapy. The study measured minimal residual disease (MRD) by Ig/TCR PCR, flow cytometry, and *BCR* - *ABL1* RT-PCR, with clinical actions based upon a single method, in this hierarchical order. Pts with MRD ≥ 0.05% at the end of block Ib (day 78) and those with MRD 0.005-0.05% at end of Ib who remained MRD positive at any detectable level after three additional high-risk (HR) chemotherapy blocks underwent HSCT in CR1. Dasatinib treatment post HSCT was optional. The remaining pts received chemotherapy plus daily dasatinib for 2 yrs, with cranial irradiation limited to

CNS3 pts. The primary study endpoint was 3-year EFS assessed when all patients completed 3 years of follow-up.

Results: From April 2012 to May 2014, 109 pts enrolled; 3 did not meet inclusion criteria and received no trial therapy. The median age was 9.0 yrs (range 1-17), 54% were males, and 80% were Caucasian. 71% had CNS1 status at baseline, 24% CNS2, and 5% CNS3. Safety analysis included all treated pts (N=106) and efficacy analysis included all treated Ph^+ ALL pts (N=104; 2 pts were retrospectively diagnosed with blast crisis CML). The database lock date was 8/17/16; at this time all pts had completed therapy and 75% had ≥3 yrs of follow-up. Two pts discontinued dasatinib for toxicity (1 allergy and 1 prolonged myelosuppression post HSCT). Nineteen pts met study criteria for HSCT, and 15 received HSCT in CR1 (14.2% of pts). The remaining 91 pts (85.8%) received EsPhALL chemotherapy plus dasatinib without HSCT. Patients tolerated dasatinib combined with chemotherapy well. The primary toxicity was febrile neutropenia and infection: Grade 3+ febrile neutropenia occurred in 75.5% of pts, Grade 3+ sepsis in 18.9%; and Grade 3+ bacteremia in 13.2%. Elevated ALT (21.7%) and AST (10.4%) were the only non-hematologic, non-infectious Grade 3+ adverse events attributed to dasatinib reported in >10% of pts. Relevant Grade 3+ non-hematologic, non-infectious toxicities attributed to dasatinib included pleural effusion (3.8%), edema (3.8%), hemorrhage (2.8%), and cardiac failure (0.8%). No cases of pulmonary hypertension or pulmonary arterial hypertension were reported. All 104 treated Ph^+ ALL pts achieved CR. As of the database lock date, 33 events had occurred including 5 deaths (3 in HR3 and 2 in reinduction) due to proven or suspected infection in the 91 patients receiving chemotherapy plus dasatinib, 2 deaths from infection post-HSCT in the 15 HSCT pts, and 26 relapses (chemotherapy 22/86; HSCT 4/12). Sites of relapse included isolated bone marrow (BM; 14), CNS (4), BM+CNS (3), BM+other (2), and other (3). At the time of the interim analysis the 3-yr EFS is 66.0% (95% CI, 54.8-75.0) and the 3-yr OS is 92.3% (95% CI, 85.2-96.1); updated results with all patients having at least 3 years of follow-up will be presented.

Conclusions: Addition of dasatinib to the EsPhALL chemotherapy regimen is safe and effective in pediatric Ph^+ ALL pts. With only 14% of pts undergoing SCT in CR1, as compared to 80% in the EsPhALL imatinib trial, this trial demonstrates similar outcomes with 3-yr EFS/OS 66.0%/92.3% in this trial vs. published 4-yr EFS/OS 61.9%/72.1% in the EsPhALL imatinib trial.

Disclosures

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Author notes

*Asterisk with author names denotes non-ASH members.

 This icon denotes a clinically relevant abstract