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ACUTE MYELOID LEUKEMIA - THERAPY, EXCLUDING TRANSPLANTATION: BIOLOGICALLY DIRECTED THERAPY OF ACUTE MYELOID LEUKEMIA

Preliminary Results of Southwest Oncology Group Study S0106: An International Intergroup Phase 3 Randomized Trial Comparing the Addition of Gemtuzumab Ozogamicin to Standard Induction Therapy Versus Standard Induction Therapy Followed by a Second Randomization to Post-Consolidation Gemtuzumab Ozogamicin Versus No Additional Therapy for Previously Untreated Acute Myeloid Leukemia.

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Abstract 790

Study **S0106** is an open-label randomized phase III trial to evaluate the benefit and toxicity of adding Gemtuzumab ozogamicin [GO] to standard induction therapy, followed by a post-consolidation randomization to receive either 3 additional doses of GO or no additional therapy [OBS]. Eligible patients were adults (age 18-60) with previously untreated de novo nonM3 AML. Patients were randomized (stratified by age <35 vs 35+) to receive induction therapy with daunorubicin (45 mg/m² D1,2,3) and cytarabine (100mg/m²/d CI D1-7) and GO (6 mg/m² D4) [AD+GO] (DeAngelo,2003) versus standard induction therapy with daunorubicin (60 mg/m² IV D1,2,3) and cytarabine (100mg/m²/d CI D1-7) [AD]. Patients in either arm who failed to achieve aplasia at D14 were retreated with AD. Patients achieving CR received consolidation therapy with 3 courses of high dose cytarabine (3 gm/m²/q12h D1,3,5 every 28 days). Patients remaining in CR after consolidation were eligible for a second randomization (stratified by cytogenetic risk category at diagnosis and use of GO during induction) between 3 doses of GO (5 mg/m² every 28 days) or OBS.

627 patients were registered on study **S0106** from May 15, 2004 though July 23, 2009, the cutoff for the second interim analysis of induction outcomes (which by protocol plan was based on the first 456 eligible patients) and first planned interim analysis of disease-free survival measured from the post-consolidation randomization [DFS] (based on the first 64 relapses or deaths). Complete response [CR] rates were 150/277=66% (AD+GO) and 159/229=69% (AD), ruling out the originally hypothesized 12% increase with AD+GO at the prespecified significance level (P<0.0025). Including CRs with incomplete hematologic recovery, the response rates were 74% in both arms. Importantly, relapse-free survival measured from the date of CR [RFS] was not significantly better in the AD+GO arm (hazard ratio [HR]=1.00, 95% confidence interval [CI] 0.69-1.44, P=0.50), unlike preliminary results of the MRC AML15 trial (Burnett, Blood 2006 108: Abstract 13). Among all patients evaluable for induction toxicity, the rate of fatal adverse events [AEs] at least possibly attributable to treatment (most commonly hemorrhage, infection and/or ARDS) was

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significantly higher in the AD+GO arm (15/260=5.8% vs 2/255=0.8%, P=0.002). One death in the AD+GO arm was attributable to sinusoidal obstruction syndrome (SOS). Notably, the AE rate in the AD+GO arm is similar to previous SWOG AML trials, while the rate in the AD arm is remarkably low (CI 0.1-2.8%). The first planned interim analysis of post-consolidation therapy evaluated 150 patients randomized between GO and OBS, only 7 of whom had unfavorable cytogenetics. 36 GO and 25 OBS patients have relapsed, and one GO and 2 OBS patients have died without report of relapse. DFS was not significantly better in the GO arm (HR=0.66 for OBS compared to GO, CI 0.40-1.08, one-sided P=0.95); moreover the hypothesized benefit of GO (HR=1.5) was rejected at the prespecified significance level (P<0.001). Based on these results – the lack of improvement in CR rate or RFS and the higher fatal induction AE rate on the AD+GO induction arm, and the lack of improvement in DFS on the post-consolidation GO arm – the SWOG DSMC on August 11, 2009 recommended closure of both the induction and post-consolidation randomizations. Among all eligible patients with any follow-up, the estimated median overall survival from study entry was 31 months with AD+GO induction (CI 22-39 months) and 35 months with AD (CI 24-41 months).

In this study, the addition of GO to induction therapy or as post-consolidation therapy did not improve the CR rate, RFS, post-consolidation DFS, or overall survival, but was associated with a significantly higher risk of fatal induction adverse events.

Disclosures: No relevant conflicts of interest to declare.

Footnotes

* Asterisk with author names denotes non-ASH members.

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