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Improved Overall Survival with Gemtuzumab Ozogamicin (GO) Compared with Best Supportive Care (BSC) in Elderly Patients with Untreated Acute Myeloid Leukemia (AML) Not Considered Fit for Intensive Chemotherapy: Final Results from the Randomized Phase III Study (AML-19) of the EORTC and Gimema Leukemia Groups

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Abstract

Background: An unmet medical need persists for elderly patients (pts) with AML who are deemed not to be fit for intensive chemotherapy. Such pts are usually treated with BSC and hydroxyurea or low-dose cytarabine, but outcomes are dismal. The immunoconjugate GO has shown single agent efficacy and tolerability in older pts with relapsed AML. The AML-19 study was designed as a sequential phase II/III trial comparing GO monotherapy to BSC (including hydroxyurea if clinically indicated) in pts age ≥ 61 yrs with previously untreated AML who were considered unfit for intensive chemotherapy (or refused it). Of the two induction schedules of GO (total dose 9 mg/m^2 delivered in 2 or 3 fractions over one week) under comparison in the phase II part of the study, the 2-fraction regimen was found to have the best efficacy profile to warrant phase III comparison with BSC (BJH 2010; 149:376). We herein report the final results of the phase III part of the study.

Methods: Untreated pts with de novo or secondary AML, adequate renal and hepatic function, and WBC count <30x10^9/L at baseline (a short course of hydroxyurea permitted) were centrally randomized 1:1 (stratified by age, WHO PS, CD33 expression on marrow blasts, WBC at diagnosis, and center) to

receive either a single induction course of GO (6 mg/m^2 day 1 and 3 mg/m^2 day 8) or BSC. Pts with no evidence of disease progression following GO induction could receive up to 8 monthly infusions of the drug at 2 mg/m^2. The primary objective of the study was to compare overall survival (OS) in the two groups. A total of 210 deaths was required in order to detect a hazard ratio (HR) of 0.63 for OS, with 90% power and 2-sided alpha=5%.

Results: Between 11/2004 and 03/2013, 237 pts were randomized from 35 European sites. The intention-to-treat population comprised 118 pts in the GO arm and 119 in the BSC arm. The median age was 77 years (range 62-88) with 64% of pts over 75 years. Baseline characteristics were well balanced between arms. At the final analysis (05/2014 cutoff), 228 deaths occurred: 113/118 (95.8%) in the GO arm, and 115/119 (96.6%) in the BSC arm. GO significantly improved OS (median 4.9 vs 3.6 months; 45.9% vs 29% alive at 6 months; 24.3% vs 9.7% alive at 1 year; 10.3% vs 6.9% alive at 1.5 year; HR, 0.69; 95% CI, 0.53-0.90; P=0.005) compared with BSC. Subgroup analyses based on stratification factors and other baseline characteristics showed that the OS benefit was generally consistent among subgroups, with a greater effect seen in pts with good/intermediate cytogenetics (median 7.3 vs 3.8 months; HR, 0.48; 99% CI, 0.31-0.75), in those with high CD33 expression (≥81% positive blasts; median 5.5 vs 3.8 months; HR, 0.47; 99% CI, 0.30-0.74), as well as in those with secondary AML (median 7 vs 4 months; HR, 0.55; 99% CI, 0.33-0.91). Among 111 pts who received at least the first dose of GO, the overall complete response rate was 27% (CR 15.3%, CRi 11.7%), and the overall disease control rate (including PR in 5.4% and stable disease for >30 days in 24.3%) was 56.7%. Of the 30 pts who achieved CR/CRi, 28 later relapsed or died in remission (1 infection, 2 general physical deterioration, 2 unknown cause), and the median disease-free survival (DFS) was 5.3 months with a 1-year DFS of 20%. CR/CRi pts had a median survival from remission of 8.2 months, with 40% alive at 1 year. The 30-day all-cause mortality from randomization was comparable in the GO (10.8%) and BSC (13.5%) arms. Most frequent grade 3+ non-hematologic adverse events (AEs) for GO vs BSC were infection (35.1% vs 34.3%), febrile neutropenia (18% vs 23.7%), bleeding (12.6% vs 12.3%), fatigue (11.7% vs 21%), and cardiac toxicity (6.3% vs 14%). Severe liver dysfunction occurred infrequently (2.7% vs 1.8% for GO vs BSC), and no episodes of VOD were reported. Overall, AEs led to GO discontinuation or death in 27 pts (24.3%).

Conclusions: Compared with BSC including hydroxyurea as necessary, single agent GO in the dose/schedule chosen significantly improved OS in elderly AML pts not considered fit for intensive chemotherapy, with an acceptable safety profile. Of note, estimates of the benefit of GO were greater in pts presenting with better-risk cytogenetics, high CD33 expression on blast cells, or secondary disease.

Disclosures Off Label Use: Gemtuzumab Ozogamicin in AML.

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