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S125 10-DAY DECITABINE VS. CONVENTIONAL CHEMOTHERAPY ("3+7") FOLLOWED BY ALLOGRAFTING (HSCT) IN AML PATIENTS ≥60 YEARS: A RANDOMIZED PHASE III STUDY OF THE EORTC LEUKEMIA GROUP, GIMEMA, CELG, AND GMDS-SG

Topic: 04. Acute myeloid leukemia - Clinical

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Background:

Older, fit AML patients (pts) treated with induction chemotherapy (IC) have poor long-term survival unless HSCT is performed. DNA-hypomethylating agents have become the backbone of AML therapy in pts unfit for IC. Promising outcomes have been reported for the 10-day decitabine (DEC) schedule, suggesting it may be a better treatment prior to HSCT as compared to IC.

Aims:

To compare efficacy and safety of 10-day DEC followed by allografting to IC followed by allografting in older fit AML pts.

Methods:

This was an international open-label randomized phase III trial (NCT02172872). Key inclusion criteria were newly diagnosed AML, age >60 years, eligible for IC, WHO performance status 0-2. DEC was administered 10 days

consecutively in cycle 1 (20 mg/m^2), 10 or 5 days in subsequent cycles (depending on bone marrow blast clearance at day 28). IC treatment was daunorubicin 60 mg/m^2 x 3 days, cytarabine 200 mg/m^2 x 7 days, followed by 1-3 additional chemotherapy cycles. Pts who had an HLA-matched donor and at least stable disease were encouraged to undergo HSCT after >1 treatment cycle. Pts from the DEC arm not receiving HSCT could continue DEC treatment. The primary endpoint was overall survival (OS). Pts were randomized 1:1, stratified by *de novo* AML vs. secondary AML, age (60-64 vs 65-70 vs >70 yrs), and institution. The statistical design aimed to detect a hazard ratio (HR) for OS of 0.75 (HR<1 indicates longer survival for DEC), requiring 441 deaths (one-sided alpha 0.025, 85% power). Due to the slow accumulation of deaths, the final analysis was performed with a clinical cut-off (CCO) date June 30, 2021, following the Data Monitoring Committee recommendation.

Results:

Between 12/2014 and 8/2019, 606 pts were randomized, 303 in each arm. Median follow-up was 4.0 yrs. Median age was 68 yrs (range 60-81), 34% of pts were ≥70 yrs old and 57% were male, 21% and 32% had good and adverse ELN 2017 risk profile, respectively. A median of 3 DEC cycles (Q1-3: 2-5) and 2 IC cycles (Q1-3: 1-2) were administered. The CR/CRi rate was 48% with DEC and 61% with IC. HSCT as part of the protocol was performed in 122 pts (40%, 30 of them not in CR/CRi) from the DEC and 118 (39%, 11 of them not in CR/CRi) from the IC arm, and in 52% in both arms at any time. By the CCO, 423 deaths occurred. The OS was not significantly different between DEC and IC groups (HR=1.04, 95% confidence interval [CI]: 0.86-1.26; 2-sided p=0.68). The median OS was 15 months (95% CI: 13-18) in the DEC and 18 months (95% CI: 14-22) in the IC group. The OS rates (%) after 1, 2, 3 and 4 years for the DEC and IC groups were 58 vs 59, 38 vs 40, 30 vs 33, and 26 vs 30, respectively. In age subgroups, the estimated HR for OS for DEC vs IC was 1.34 (99% CI: 0.79-2.28) for pts aged 60-64, 1.14 (99% CI: 0.77-1.69) for pts aged 65-69, and 0.84 (99% CI: 0.55-1.26) for pts aged >70 yrs (p-value for trend: 0.058). Notable differences in the incidence of grade 3-5 adverse events (%) reported (before HSCT) were: febrile neutropenia (37% for DEC vs 57% for IC), decrease in platelets (24% for DEC vs 32 % for IC), oral mucositis (2% for DEC vs 10% for IC), diarrhea (1% for DEC vs 8% for IC), decrease in neutrophils (19% for DEC vs 13% for IC). The 30-day mortality rate was 3.6% for DEC and 6.4% for IC. The incidence of grade 5 treatment-related adverse events after HSCT was comparable in both treatment arms (25% for DEC and 22% for IC).

Summary/Conclusion:

Treatment with DEC resulted in a similar OS and HSCT rate but a better safety profile compared to IC in older AML pts ≥60 yrs, eligible for IC.