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General AML

Venetoclax combined with low-dose cytarabine for elderly patients with untreated AML

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Older patients with acute myeloid leukemia (AML) are often unable to tolerate intensive chemotherapy (IC), and so have limited treatment options.[1] Less intensive options, such as low-dose cytarabine (LDAC) have been associated with poor response rates.[2] There is currently an unmet need for more effective and less toxic treatment options for older patients with AML.

Associate Professor Andrew Wei, from The Alfred Hospital, Melbourne, AU, and colleagues conducted an open-label, multicenter, multinational, dose-escalation/dose-expansion phase Ib/II trial (NCT02287233) investigating the safety and preliminary efficacy of venetoclax,[3] a selective B cell leukemia inhibitor, together with LDAC in older patients with AML, ineligible for intensive chemotherapy. Patients were accepted into the study providing they had no prior treatments for their AML, except for hypomethylating agents (HMA). The primary objectives of the study were safety, pharmacokinetics (PK), maximum tolerated dose and recommended phase II dose of venetoclax.

The key endpoints of the study were safety, tolerability, safety, response rates, duration of response (DOR) and overall survival (OS). Objectives of dose expansion were to obtain preliminary estimates of efficacy, including: overall response rate (ORR), complete remission (CR), and complete remission with incomplete blood count recovery (CRi).

Patient Characteristics

- N = 82
- Median age: 74 (range, 63—90)
- Patients with:
  - Secondary AML: 49%
  - Prior HMA treatment: 29%
  - Poor-risk cytogenetic features: 32%
  - Baseline mutations: TP53 (14%), FLT3 (23%), IDH1/2 (25%), NPM1 (13%)

Treatment

- Tumor lysis syndrome (TLS) prophylaxis initiated >24 hours prior to the first dose of venetoclax
- Venetoclax administered once daily, orally, after food, for 28-day cycles
- Venetoclax dosing began at 50mg or 100mg and then increased over 4—5 days to the recommended phase II dose of 600mg
- LDAC (20 mg/m^2) administered subcutaneously, on days 1—10

- Patients in CR with neutropenia and/or thrombocytopenia had a treatment interruption until the neutrophil count reached ≥5 x 10^9/L, and platelet count was ≥25 x 10^9/L
- Patients with concomitant use of CYP3A inhibitors requiring venetoclax dose adjustments: 50%

Results

Table 1: Adverse Events (AEs) affecting >20% of patients, with 55% of patients needing venetoclax dose interruptions due to AEs

AEs	**Patients (%)**
Febrile neutropenia	34 (42)
Thrombocytopenia	31 (38)
Decreased WBC count	28 (34)
Anemia	22 (27)
Neutropenia	22 (27)
Platelet count decreased	20 (24)

Table 2: Serious AEs affecting >5% of patients

Serious AEs	**Patients (%)**
Anemia	25 (31)
Febrile neutropenia	22 (27)
Pneumonia	8 (10)

AML progression	7 (9)
Sepsis	6 (7)

Table 3: CR and CRi rates by patient subgroups

		Rate of response (%)	
		CR	**CRi**
All		26	28
Cytogenic risk	Intermediate	35	29
	Poor	15	27
Prior HMA	Yes	4	29
	No	34	28
AML	De Novo	45	26
	Secondary	5	30

Key Findings

- Median duration of remission for patients achieving CR/CRi after venetoclax and LDAC: 8.1 months (95% CI, 5.3—14.9)
- Median OS for all patients: 10.1 months (95% CI, 5.7—14.2)
- 12-month estimated survival for patients achieving CR (100%), CRi (49%), CR/CRi (73%), or no response was (5%)
- Median OS was longer in patients without prior HMA exposure (13.5 months, 95% CI, 7.0—18.4) compared with those previously exposed to prior HMA (4.1 months; 95% CI, 2.9—10.1)

Conclusion

The combination of venetoclax and LDAC is tolerable and associated with high rates of remission in elderly patients with previously untreated AML. The rapid induction and durable length of remission make this combination an attractive treatment option for patients ineligible for intensive chemotherapy.

References

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3. Wei A.H. *et al*. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. *Journal of Clinical Oncology*. 2019 Mar 20. DOI: 10.1200/JCO.18.01600