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ORAL ABSTRACTS

632.CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Phase 2 Study of Dasatinib with and without Venetoclax in Patients with Early Chronic Phase Chronic Myeloid Leukemia (ECP-CML)

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Background

Treatment-free remission (TFR) is a therapeutic goal for patients with ECP-CML once patients maintain a deep molecular remission (DMR) on tyrosine kinase inhibitors (TKIs). Only a fraction of patients (pts) achieved sustained (3+ years) molecular remission with 4.0- to 4.5-log reduction (MR4.5). Preclinical studies showed that BCL-2 is a key survival factor for CML stem/progenitor cells. Therefore, the combination of TKIs and venetoclax, targeting *BCR::ABL1* and BCL-2, has the potential to significantly improve DMR and subsequently the rates of TFR. The aim of this study is to evaluate the safety and efficacy of the combination.

Methods

Patients with ECP-CML or accelerated phase (AP; defined by clonal evolution only) were eligible; pts with < 1 month of prior TKI therapy were eligible. Pts received single-agent dasatinib 50 mg/d for the first 3 months. From Month 4 and onwards, venetoclax was administered from Days 1 to 14 each month concomitantly with dasatinib for a total of 3 years. The first 16 patients received venetoclax 200 mg/d, with a rapid ramp-up starting 50 mg on Day 1, then 100 mg on Day 2, then 200 mg daily on Day 3 and onwards. Due to neutropenia observed with continuous dose of venetoclax 200 mg/d, the protocol was ameded: from patient #17 and onwards, venetoclax was administered at 200 mg/d for 14 days per month and upon achievement of MR4.5, venetoclax was reduced to 100 mg/d for 7 days per month. After 3 years of combination, patients received single-agent dasatinib. TFR was offered after ≥ 3 years of DMR. The primary endpoint was the rate of major molecular response (MMR) by 12 months of the combination. The secondary endpoints were the 12-month rate of MR4.5 and the cumulative overall rate of MR4.5; the rates of MR4.5 at 6-, 12-, 18-, 24, and 36-months of the combination; the proportion of patients with sustained MR4.5 of 3 years and more; the TFR rate; overall survival; and the safety of the combination. Cumulative response rates were calculated with treatment failure as a competing event. Failure-free survival (FFS) was calculated from the initiation of therapy to loss of major cytogenetic response (MCyR), transformation to AP or blast phase, discontinuation of therapy for any reason except of TFR, or death.

Results

Sixty-five pts were enrolled and treated between April 2018 and August 2021. The median age at treatment initation was 46 years (range, 23-73) and 57% of the pts were females. Twenty-one (32%) pts had splenomegaly, 46 (71%) had low Sokal risk disease and 3 (5%) had high Sokal risk disease **(Table 1)**. By 12 months of the combination, 85% of the pts had achieved MMR or deeper response. The median time to MMR, MR4, and MR4.5 were 6.2 months, 13 months, and 23.9 months from the time of TKI start, respectively. After a median follow-up of 25.7 months (range, 8.7-48.1), two pts discontinued therapy due to

adverse events (GI intolerance, and pleural effusion); the 2 -year FFS was 96%. One pt switched TKI therapy due to the lack of 18-month complete cytogenetic response (CCyR); no loss of CCyR, transformation, or death was observed.

We then compared the outcomes with the combination to the outcomes of 85 pts treated with single-agent dasatinib. From the start of TKI therapy, the 12-month cumulative MMR rates were 78% and 79% in the dasatinib single-agent and dasatinib + venetoclax groups, respectively. The cumulative 24-month rates of CCyR, MMR, MR4, and MR4.5 are summarized in **Table 2**. In the dasatinib single-agent group, 3 pts switched TKI therapy due to the lack of 12-month MCyR, 18-month CCyR, and the acquisition of ABL1 mutation (1 each); 3 pts switched TKI therapy due to loss of CCyR; 2 pts died during therapy (deaths unrelated to CML).

Within one year of therapy, the incidence of grade 1/2 neutropenia (absolute neutrophil count, below lower range of normal to 1,000 x10^9/L) was 21% and 52% in the dasatinib single agent and dasatinib + venetoclax groups, respectively ($P<0.001$); the incidence of grade 3/4 neutropenia (absolute neutrophil count, below 1,000 x10^9/L) was 8% and 17%, respectively ($P<0.001$). There was no incidence of neutropenic fever in the dasatinib + venetoclax.

Conclusion

The combination of dasatinib 50 mg/d and venetoclax is safe and effective in pts with ECP-CML. With a median follow-up of 2 years, the cumulative resposne of dasatinib + venetoclax is similar to that of dasatinib single-agent without adding significant toxicities. Further follow-up is needed for the evaluation of TFR.

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Table 1. Patient characteristics

No. (%) / Median (range)	All N = 150	Dasatinib Single-agent N = 85	Dasatinib + Venetoclax N= 65	P
Age (year)	47 (19.9-80.7)	47 (19.9-80.7)	46 (23.1-72.8)	0.079
Female	69 (46)	44 (52)	37 (57)	0.530
Performance status				
0-1	149 (99)	84 (99)	65 (100)	0.567
2+	1 (1)	1 (1)	0	
Spleen size on examination	0 (0-20)	0 (0-15)	0 (0-20)	0.014
Splenomegaly on examination	35 (23)	14 (17)	21 (32)	0.023
Laboratory results				
White blood cell count ($\times 10^6$/L)	28.0 (1.7-290.8)	29.5 (2.5-290.8)	26.1 (1.7-215.3)	0.597
Hemoglobin ($\times 10$ g/L)	11.9 (7.0-17.1)	12.1 (7.0-17.1)	11.6 (8.2-16.4)	0.281
Platelet count ($\times 10^6$/L)	334 (63-1956)	337 (98-1956)	319 (63-1191)	0.965
% blasts in bone marrow	2 (0-9)	1 (0-9)	2 (0-7)	0.012
% basophils in bone marrow	1 (0-11)	1 (0-11)	2 (0-8)	0.164
Clonal evolution	7 (5)	5 (6)	2 (3)	0.345
Transcript type				
B2A2	62 (41)	32 (38)	30 (46)	0.305
B2A2 + B3A2	29 (19)	15 (18)	14 (22)	
B3A2	59 (39)	38 (45)	21 (32)	
Sokal risk				
Low	101 (67)	55 (65)	46 (71)	0.733
Intermediate	41 (27)	25 (29)	16 (25)	
High	8 (5)	5 (6)	3 (5)	

Table 2. Cumulative response rates from the start of TKI therapy

Responses	Dasatinib-single agent N=85	Dasatinib + Venetoclax N=65	*P*
Cumulative 12-month MMR, %	78	79	0.68
Cumulative 24-month CCyR, %	94	97	0.68
Cumulative 24-month MMR, %	88	93	0.76
Cumulative 24-month MR4, %	70	64	0.93
Cumulative 24-month MR4.5, %	63	53	0.62
Cumulative 24-month CMR, %	46	49	0.60
Survival			
2-year failure-free survival, %	92	96	0.13

Figure 1

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