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Phase I/II study of low-dose azacytidine in patients with chronic myeloid leukemia who have minimal residual disease while receiving therapy with tyrosine kinase inhibitors

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The depth of molecular response achieved with tyrosine kinase inhibitor (TKI) therapy in patients with chronic myeloid leukemia (CML) may improve the long-term outcome. Among patients who achieve complete cytogenetic response (CCyR), those who do not achieve a major molecular response (MMR) have a seven-year event free survival (EFS) of 50% compared to 85% for those who achieved MMR and 95% for those with MR4.5.[1] There is also a trend for improved relative survival for those with the deepest response.[2] Furthermore, those with the deepest responses might be eligible for elective treatment discontinuation.[3] Hence, improving the depth of molecular response has become an important goal of therapy in CML.

Hypermethylation of abl, bcr, cadherin-13, and p15, among others, have been reported in CML and is associated with worse outcomes.[4–9] Preclinical studies have demonstrated synergy between imatinib and hypomethylating agents like decitabine.[10,11] Hypomethylating agents have been studied in patients with advanced CML and in patients who have failed TKIs, and has shown clinical activity as a single agent and in combination with TKIs.[12,13] We hypothesized that adding low-dose azacytidine (AZA) to a TKI may improve the depth of molecular response in CML patients with CCyR.

We conducted a single arm open label phase I/II trial to evaluate the toxicity and efficacy of low-dose AZA in CML patients with CCyR who have persistent molecular minimal residual disease (MRD, detected with quantitative real time polymerase chain reaction) while receiving TKIs (NCT01460498). For the phase I portion of the study, patients were eligible for enrollment regardless of the level of BCR-ABL transcript. For phase II part of the study, patient needed to have detectable BCR-ABL transcript levels on two consecutive measurements one month apart, either increased by any value for patients who had never

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achieved MMR, or increased by at least 1-log leading to loss of MMR. Adult patients with BCR/ABL-positive CML and ECOG performance status ≤2 who had CCyR were eligible for this trial. The European LeukemiaNet criteria were used for staging and response assessment.[14] Patients needed to be on TKI therapy for at least 18 months, and stable TKI dose for at least 6 months prior to enrollment. Patients received AZA 50 mg/m^2/day subcutaneously or intravenously for three days every four weeks. Patients continued on the same dose of the TKI they were receiving up to the time of enrollment. The study was halted after three patients were enrolled because of slow accrual.

The enrolled patients included one man and two women, aged 56, 56, and 72 years, respectively. The baseline characteristics and outcomes are shown in Table 1. Two patients had been initially diagnosed in chronic phase (CP) and one in accelerated phase (AP) by blast percentage and cytogenetic clonal evolution (CE). Two patients had initially received therapy with imatinib and later switched to dasatinib 100 mg daily after 36.5 and 30.4 months, respectively, one for transformation to AP by CE criteria, and one for unknown reasons (medication change before coming to our institution). The other patient was initially on dasatinib for 6.4 months and was later changed to imatinib 400 mg twice daily prior to referral to our institution due to concerns about drug absorption given her prior history of gastric bypass surgery. All patients confirmed (verbally) full adherence to treatment prior to enrollment.

The enrolled patients have received 38, 27, and 19 cycles of AZA. All continue on therapy: two at the starting dose of AZA 50 mg/m^2 and one at a reduced dose (due to recurrent neutropenia) of 25 mg/m^2 for three days every six weeks. The latter patient also developed grade one myalgia, grade one chest pain, and subconjunctival hemorrhage. She also had mild anemia and moderate neutropenia before starting AZA; grade 1/2 anemia and grade 1–4 neutropenia has persisted throughout the course of treatment. A total of 18 adverse events (AE) were recorded, five of them related to AZA and all grade 1 or 2 (myalgia, constipation, gastrointestinal hemorrhage, edema, and chest pain, one each). Hematologic toxicities were confounded by preexisting cytopenias prior to the start of AZA. Patient 3 had mild dysplastic features on bone marrow biopsy prior to, and throughout the clinical trial. She also had trisomy 8 in 1/20 and 2/20 meta-phases in two consecutive bone marrow samples prior to starting on clinical trial. The cytogenetic abnormality resolved, but she continued to have mild dysplastic features. There have been no serious AEs.

All three patients had detectable MRD with transcript levels of 1.73 IS, 1.25 IS, and 0.11 IS, after 89, 29, and 62 months on TKI, respectively. Addition of low dose AZA caused steady decline in MRD (Figure 1). All patients achieved MMR after a median of 10.1 months (range 0.9–13.5 months). At the time of this analysis, all patients continue to maintain MMR for 23.6, 17.0, and 24.0 months. All patients achieved MR4.5 after 19.8, 27.0, and 4.4 months on study. One patient achieved MR4.5 on last follow-up while the other two patients continue to be in MR4.5 for total duration of 15.2 and 13.6 months, respectively.

The major limitation of our study was small sample size due to slow accrual. The need for injections was the main reason that discouraged patients to enroll. Due to the low enrollment, the maximum tolerated dose for AZA when used in combination with a TKI

could not be determined. However, the dose tested appeared safe in this limited sample. Our patients had persistent molecular MRD despite being on TKIs for over 2–7 years, and achieved sustained MMR and MR4.5 after addition of AZA. These trends in the transcript levels are encouraging and suggest a possible role of hypomethylating agents in treating molecular MRD in patients in whom TKI alone has not been sufficient to achieve MR4.5. Other similar strategies using a TKI in combination with another agent for suboptimal responders are being investigated. These include arsenic trioxide (NCT01397734), ruxolitinib (NCT01751425), BL-8040 (NCT02115672), and hydroxy-chloroquine (NCT01227135). The actual efficacy and safety of AZA in this setting cannot be properly assessed with the patients reported here. However, given these preliminary observations, this approach merits further investigation. The availability of oral AZA [15] may make it more appealing for patients to consider such an approach.

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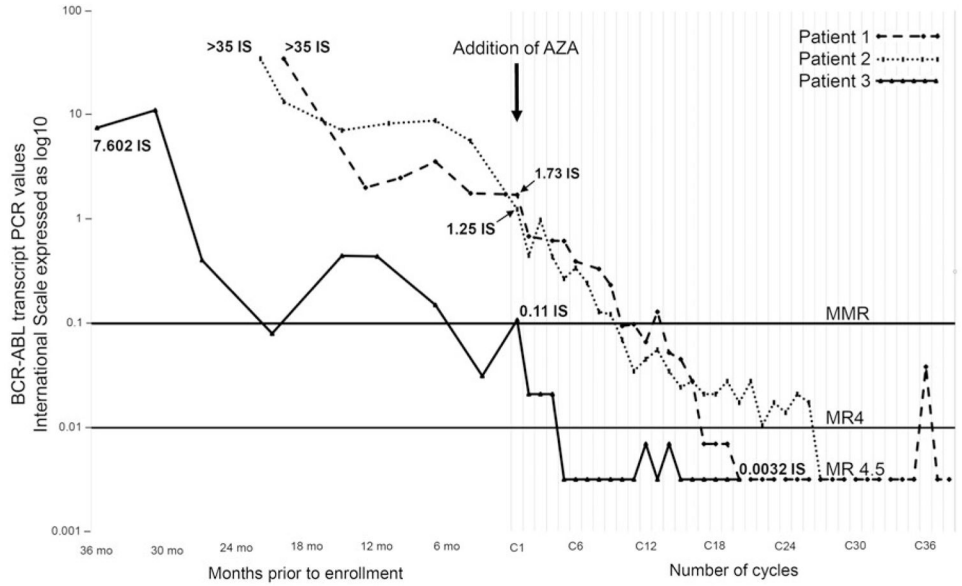

Figure 1.

Trends of BCR-ABL transcripts prior to enrollment and while on clinical trial receiving AZA-TKI.

Table 1

Baseline characteristics and outcomes in the three patients.

Variables	Patient 1	Patient 2	Patient 3	Reference ranges	Units
Age	56	56	72		Years
Sex	M	F	F		
Stage at initial diagnosis	CP	CP	AP[a]		
Variables prior to enrollment on trial					
Hemoglobin	131	98	105	140–180 for men, 95–133 for women	g/L
Absolute neutrophil count	2.4	1.76	0.82	1.7–7.3	$\times 10^9$/L
Platelet count	175	97	110	140–440	$\times 10^9$/L
ABL kinase domain mutation analysis	No mutations identified	No mutations identified	Testing canceled due to MRD of 0.448 IS		
Bone marrow morphology	Trilineage hematopoiesis, no evidence of CML	Cellular marrow (50%) with trilineage hematopoiesis, no evidence of CML	Cellular (30%) marrow with dyspoietic trilineage hematopoiesis; 1% blasts		
Conventional cytogenetics (% of normal metaphases)	100	100	90% (2 metaphases with trisomy 8)		
Treatment related variables					
Duration on frontline TKI	36.5	6.4	30.4		Months
Duration on second line TKI	52.7	23	31.5		Months
Duration on single agent TKI	89.2	29.4	61.9		Months
Duration on TKI and AZA	37.1	27.0	25.0		Months
No. of cycles of AZA	38	27	19		
Duration of cycles	28 (26–43)	28 (27–41)	35 (27–63)		Days (range)
BCR-ABL transcript level at enrollment	1.7255	1.2495	0.1085		International Scale
Outcome related variables					
BCR-ABL transcript levels at last follow up	0.0032	0.0032	0.0032		International Scale
Time to achieve sustained MMR	13.5	10.1	0.9		Months
Duration of MMR	23.6	17.0	24.0		Months
Time to achieve MR4.5	19.8	27.0	4.4		Months
Total duration of MR4.5	15.2	NA	13.6		Months
Variables while on AZA-TKI combination[b]					

Variables	Patient 1	Patient 2	Patient 3	Reference ranges	Units
Hemoglobin	125 (116–132)	104 (91–109)	94 (86–102)	140–180 for men, 95–133 for women	g/L
Absolute neutrophil count	2.13 (1.57–3.74)	1.7 (1.31–2.7)	0.64 (0.34–1.31)	1.7–7.3	$\times 10^9$/L
Platelet count	206 (123–289)	147 (86–172)	140 (107–176)	140–440	$\times 10^9$/L
Bone marrow morphology at six months	Cellular marrow with adequate trilineage maturation	Cellular marrow (30–40%) with mild erythroid hyperplasia. No morphologic evidence of CML	Hypocellular marrow (15–20%) with mild dysgranulopoiesis and mild dyserythropoiesis[c]		
Conventional cytogenetics at 6 months (% of normal metaphases)	100	100	100[c]		

[a] By blasts and clonal evolution criteria.

[b] Where applicable, values measured at the end of the cycle; expressed as median and range.

[c] At nine months.

NA: not applicable.