LATE EFFECTS OF TYROSINE-KINASE INHIBITORS IN PEDIATRIC LEUKEMIAS

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Background: Tyrosine kinase inhibitors (TKIs) improve outcomes for Philadelphia chromosome (Ph)-positive chronic myelogenous leukemia (CML), Ph+ acute lymphoblastic leukemia (ALL), and cancers with ABL-class gene rearrangements or mutations in the JAK-STAT pathway, i.e. Ph-like ALL. However, little is known about the impact of long-term TKI exposure. Our objective was to assess the incidence and type of late-onset TKI-related toxicities in children with Ph+/Ph-like ALL or CML.

Materials/Methods: We performed a retrospective chart review of patients under 21 years old diagnosed with CML or Ph+/Ph-like ALL at Texas Children's Cancer Center from 2006-2019 and prescribed one or more TKI. An initial data set was derived using TKI prescribing data, followed by exclusion of patients treated with stem cell transplant (SCT) and those who never achieved a durable remission. Late effects data capture began on the last day of combination chemotherapy for ALL and one year after diagnosis for CML. Events related to TKI exposure were manually abstracted from the electronic medical record. Descriptive statistics were used to stratify outcomes by diagnosis, exposure to specific TKIs, and TKI use during the data capture period.

Results: Forty-nine TKI-exposed patients were identified. Three were excluded for insufficient data, 15 for SCT, and 1 for relapsed/refractory disease. Of the 30 remaining, 22 had CML, 7 had Ph+ ALL, and 1 had Ph-like ALL. The median follow-up was 6.3 years (range 2.2-14.3). Prior to initiation of data capture, 40% of patients were treated with dasatinib alone, 33% with imatinib, and 27% with multiple TKIs. During the data capture period, 47% were treated with dasatinib alone, 27% with imatinib, 13% with multiple TKIs, and 13% with no TKI. All pericardial (n=3) or pleural (n=3) effusion outcomes occurred in patients that continued to receive a TKI during the data capture period. Other observed outcomes included hypertension (n=3), ectopy on electrocardiogram (ECG) (n=3), and gastrointestinal bleed (n=2). No differences were noted in outcome incidence by diagnosis or TKI exposure type.

Conclusions: TKIs have substantially impacted prognosis for subsets of childhood leukemia, but there are no long-term data to inform exposure-based late effects risk and screening. Our data suggests that TKI-exposed survivors may be at risk for TKI-related late effects, particularly those receiving ongoing treatment.

Images / Graph / Table

Table 1: TKI-related outcomes among childhood ALL patients that completed combination chemotherapy and CML patients at least one year from diagnosis.

	Incidence of outcomes during data capture			TKI Exposure			TKI use during data capture	
	Total (n=30)	ALL (n=8)	CML (n=22)	Dasatinib only (n=12)	Imatinib only (n=8)	Multiple (n=10)	On TKI (n=26)	Not on TKI (n=3)
BMI Category at Follow up								
Normal Weight, n (%)	10 (33.3)	5 (62.5)	5 (22.7)	4 (33.3)	3 (37.5)	3 (30.0)	8 (30.8)	2 (50.0)
Overweight, n (%)	10 (33.3)	2 (25.0)	8 (36.4)	4 (33.3)	3 (37.5)	3 (30.0)	8 (30.8)	2 (50.0)
Obese, n (%)	10 (33.3)	1 (12.5)	9 (40.9)	4 (33.3)	2 (25.0)	4 (40.0)	10 (38.5)	0 (0.0)
Endocrine								
Growth Hormone deficiency, n (%)	1 (3.3)	1 (12.5)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (3.9)	0 (0.)
Pancreatitis, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular								
Hypertension, n (%)	3 (10.0)	1 (12.5)	2 (9.1)	3 (25.0)	0 (0.0)	0 (0.0)	2 (7.7)	1 (25.0)
Pulmonary Hypertension, n (%)	1 (3.3)	0 (0.0)	1 (4.6)	1 (8.3)	0 (0.0)	0 (0.0)	1 (3.9)	0 (0.0)
Pericardial effusion, n (%)	3 (10.0)	0 (0.0)	3 (13.6)	3 (25.0)	0 (0.0)	0 (0.0)	3 (11.5)	0 (0.0)
Prolonged QTc*, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ectopy (PVCs or PACs)*, n (%)	3 (13.6)	1 (25.0)	2 (11.1)	1 (12.5)	2 (33.3)	0 (0.0)	2 (9.5)	1 (100.0)
Intraventricular conduction delay (QRS >100ms)*, n (%)	1 (4.6)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	1 (12.5)	1 (4.8)	0 (0.0)
Ejection fraction <55%*, n (%)	1 (4.0)	1 (16.7)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
Pulmonary								
Pleural effusion, n (%)	3 (10.0)	0 (0.0)	3 (13.6)	2 (16.7)	1 (12.5)	0 (0.0)	3 (11.5)	0 (0.0)
Hematology/bleeding								
Pulmonary hemorrhage, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal bleed, n (%)	2 (6.7)	1 (12.5)	1 (4.6)	2 (16.7)	0 (0.0)	0 (0.0)	1 (3.9)	1 (25.0)
CNS bleed, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombus, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal								
Joint effusion, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Percentages calculated based on n=22 patients with ECG and n=25 with echocardiogram
PVC = premature ventricular contraction; PAC = premature atrial contraction