# Distribution and Frequency of Tyrosine-Kinase Inhibitor-Associated Complications in Survivors of Pediatric Leukemias

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## BACKGROUND

Tyrosine kinase inhibitors (TKIs) have improved outcomes for pediatric malignancies characterized by the presence of the Philadelphia chromosome (Ph), including chronic myelogenous leukemia (CML) and acute lymphoblastic leukemia (ALL).[1] Acute and long-term toxicities of TKIs have been well-described in adult populations, but there is limited data on these effects in pediatric patients.[2] Moreover, because of this knowledge gap, TKIs are not included in current screening guidelines, resulting in substantial variation in practice for long-term follow-up care of these patients.[3]

## PURPOSE

Our objective was to assess the incidence and type of late-onset TKI-related toxicities in children treated for CML and Ph+/Ph-like ALL.

## METHODS

- Reviewed medical records from patients diagnosed between 2006 and 2019 at <21 years of age with CML or Ph+/Ph-like ALL and prescribed one or more TKIs
- Excluded patients treated with stem cell transplant or who did not achieve durable remission
- Outcomes captured from the last day of combination ALL chemotherapy or beginning at one year after CML diagnosis
- Toxicities selected *a priori* based on known adverse events associated with long-term use of TKIs in adult populations as well as limited pediatric data
- Outcome incidence described during the data capture period, stratified by diagnosis and TKI exposure

**Table 1:** Late-onset complications by diagnosis and TKI exposure during the data capture period

| | Total Incidence n (%) | Leukemia type | | Dasatinib Only | Imatinib Only | Multiple TKIs | On any TKI | Not on TKI |
|---|---|---|---|---|---|---|---|---|
| | | ALL (N=8) | CML (N=22) | (N=12) | (N=8) | (N=10) | (N=26) | (N=4) |
| **BMI Category n(%)** | | | | | | | | |
| Normal Weight | 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 | 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 | 10 (33.3) | 1 (12.5) | 9 (40.9) | 4 (33.3) | 2 (25.0) | 4 (40.0) | 10 (38.5) | 0 |
| **Endocrine** | | | | | | | | |
| GH deficiency | 1 (3.3) | 1 (12.5) | 0 | 0 | 1 (12.5) | 0 | 1 (3.9) | 0 |
| **Cardiovascular** | | | | | | | | |
| HTN | 3 (10.0) | 1 (12.5) | 2 (9.1) | 3 (25.0) | 0 | 0 | 2 (7.7) | 1 (25.0) |
| Pericardial effusion | 3 (10.0) | 0 | 3 (13.6) | 3 (25.0) | 0 | 0 | 3 (11.5) | 0 |
| **Pulmonary** | | | | | | | | |
| Pleural effusion | 3 (10.0) | 0 | 3 (13.6) | 2 (16.7) | 1 (12.5) | 0 | 3 (11.5) | 0 |
| Pulmonary HTN | 1 (3.3) | 0 | 1 (4.6) | 1 (8.3) | 0 | 0 | 1 (3.9) | 0 |
| **Hematology/bleeding** | | | | | | | | |
| GI bleed | 2 (6.7) | 1 (12.5) | 1 (4.6) | 2 (16.7) | 0 | 0 | 1 (3.9) | 1 (25.0) |

**Table 2:** ECG abnormalities prior to and during the data capture period

| | ECGs | | | Patients | | |
|---|---|---|---|---|---|---|
| **ECG finding** | **Total n=189** | **Prior to data capture period n=129** | **During data capture period n=60** | **Total* n=27** | **Prior to data capture period n=25** | **During data capture period n=23** |
| **Ectopy, n (%)** | 4 (2.1) | 1 (0.8) | 3 (5.0) | 3 (11.1) | 1 (4.0) | 3 (13.0) |
| **PACs, n (%)** | 1 (0.5) | 0 | 1 (1.7) | 1 (3.7) | 0 | 1 (4.3) |
| **PVCs, n (%)** | 3 (1.6) | 1 (0.8) | 2 (3.3) | 2 (7.4) | 1 (4.0) | 2 (8.7) |
| **IVCD (QRS >100msec), n (%)** | 1 (0.5) | 1 (0.8) | 0 | 1 (3.7) | 1 (4.0) | 0 |
| **Prolonged QTc (>450msec), n (%)** | 12 (6.3) | 12 (9.3) | 0 | 5 (18.5) | 5 (20.0) | 0 |

*Note some patients had events both prior to and during the data capture period.

## RESULTS

- 30 eligible patients identified
  - n=22 with CML
  - n=7 with Ph+ ALL and n=1 with Ph-like ALL
- Median follow-up: 6.3 years (range, 2.2-14.3)
- Long-term complications:
  - Effusions, pericardial (n=3) and pleural (n=3)
  - Hypertension (n=3)
  - Ectopy (n=3)
  - Gastrointestinal bleed (n=2)
  - Growth hormone deficiency (n=1)
- No differences in outcomes by diagnosis or TKI
- Pleural and pericardial effusions were most common, all occurring in patients that continued on TKI

## CONCLUSION

Long-term complications of TKIs are well-characterized in adult populations, but little is known regarding the long-term impact of these agents in survivors of childhood leukemia. Our results support further assessment of pulmonary, cardiac, and endocrine outcomes in larger childhood cancer survivor cohorts that continue on long-term TKI treatment. This study adds to the growing evidence of long-term TKI-associated toxicities and supports ongoing efforts to evaluate the feasibility and success of TKI discontinuation in children with CML (NCT03817398).

## REFERENCES

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