Tyrosine Kinase Inhibitor Discontinuation Syndrome

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Introduction

- Tyrosine kinase inhibitors (TKIs) have become an important therapeutic option for patients with cancer and other myeloproliferative disorders.
- TKI discontinuation is often required during treatment due to cytopenias, infections, or procedural bleeding risk.
- Abrupt TKI withdrawal can lead to a discontinuation syndrome ranging **from flu-like symptoms** to **sepsis-like features**.
- A leading theory is that the re-emergence of cytokine mediated symptoms result in an overactive state of a patient's immune system.[1]
- This overactive pro-inflammatory state can lead to a critical **shock like-syndrome, acute respiratory failure requiring intubation, DIC, and need of vasopressors**.[2,3]

Methods

- We performed a case review of two cases of TKI discontinuation syndrome.
- We conducted a literature review regarding the mechanism for TKI discontinuation syndrome and occurrence of its spectrum of presentation.

Case 1

- A 65-year-old male on **ruxolitinib** for treatment of chronic eosinophilic leukemia was admitted due to transformation to a myeloid neoplasm with excess blasts.
- At presentation, he exhibited evidence of spontaneous tumor lysis syndrome, and ruxolitinib was discontinued due to thrombocytopenia (platelets 36,000/µL).
- 3 days after ruxolitinib discontinuation, the patient clinically decompensated and was upgraded to the ICU for septic-like shock. He was hemodynamically unstable with hypotension, tachycardia, and hypoxia in addition to being febrile.
- A broad infectious workup was completed, and the patient eventually needed vasopressor support and intubation.
- Work up was negative for infection, and no etiology for the sepsis-like features was discovered other than ruxolitinib discontinuation.

Case 2

- A 79-year-old male with CLL with bulky abdominal lymphadenopathy at presentation was started on **ibrutinib** as second line therapy.
- He required outpatient procedural interventions on multiple occasions, each time discontinuing ibrutinib beforehand to reduce risk of bleeding.
- With each discontinuation of ibrutinib, the patient experienced flu-like symptoms including fevers, chills, myalgias, and fatigue.
- The patient's symptoms improved only with restarting ibrutinib.

Discussion

- Abrupt discontinuation of TKIs can cause a discontinuation syndrome presenting with features ranging from flu-like illness to sepsis-like features (fever, tachycardia, hypotension, hypoxemia). See Table 1 for a case series of ruxolitinib withdrawal syndrome published by Beauverd et al.[2]
- Features of this syndrome are most likely secondary to a **rebound cytokine storm** that occurs with abrupt discontinuation of a TKI.[1,2]

Table 1

No	Sex, Age	Disease	Clinical characteristics of RWS
0	M, 76	PMF	Recurrent fever, biological inflammatory syndrome and ARDS
1 [17]	F, 59	Post-PV MF	Respiratory distress, severe anemia requiring transfusion and symptomatic splenomegalia
2 [17]	F, 69	Post-PV MF	Respiratory distress with septic shock-like syndrome
3 [17]	M, 44	Post-PV MF	Respiratory distress associated with pleural and pericardial effusion
4 [17]	M, 64	PMF	Recurrent fever and recurrence of PMF symptoms (fatigue, pruritus, night sweats, splenomegalia with splenic infarction)
5 [17]	F, 56	Post-PV MF	Disseminated intravascular coagulation-like syndrome
6 [18]	F, 70	Post-PV MF	Recurrent fever, dyspnea, diarrhea and accelerated splenomegalia

F female, *M* male, *MF* primary myelofibrosis, *post-PV MF* post polycythemia vera myelofibrosis, *RWS* ruxolibinib withdrawal syndrome, *PMF* primary myelofibrosis, *ARDS* acute respiratory distress syndrome

Conclusions

- When feasible, **rapid discontinuation of TKIs should be avoided,** and a **monitored tapering schedule with or without the use of corticosteroids** should be in place.[2]
- Additionally, given its critical impact on a patient's health, possible TKI withdrawal should be a provider-patient discussion prior to the medication being initiated.

References

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