Death from diltiazem-ibrutinib interaction

Marissa Ryan, Christine Carrington, Belinda Badman, Nazanin Falconer.

Introduction

A 68-year-old male taking ibrutinib 560 mg daily for mantle cell lymphoma presented to ED with shortness of breath, chest pain and dizziness. He was subsequently admitted.

- diagnosis included atrial fibrillation (AF), attributed to ibrutinib therapy (the prevalence of AF is between 10 and 38% in people taking ibrutinib, compared to about 2% in the general population).
- metoprolol, digoxin, and diltiazem were started for rate control
- ibrutinib was withheld but then recommenced on discharge.

Three months post-discharge, the patient had a cardiac arrest and died 3 days later.

Research objective

To determine the optimal dosing of ibrutinib in patients commenced on diltiazem for treatment of AF.

Methods

A literature review was conducted to determine the optimal dosing of ibrutinib in the context of diltiazem and identify interactions associated with this combination. The patient's records were reviewed and causality analysis, using the Naranjo algorithm, was conducted to identify the likelihood of ibrutinib toxicity causing the fatal reaction.

Results

The Naranjo Algorithm score was 7 (probable reaction) for the ibrutinib and diltiazem interaction causing ibrutinib toxicity. The patient's arrhythmias and cardiac arrest were secondary to ibrutinib toxicity due to concomitant treatment with diltiazem. The ibrutinib dose should be reduced by 50% to 75% for patients requiring diltiazem with monitoring of clinical response and toxicities.[1,2]

Discussion

There is high potential for severe drug–drug interactions with medicines, such as diltiazem, used to treat arrhythmias.

As diltiazem is a moderate inhibitor of CYP3A4 and ibrutinib is a substrate of this enzyme, prolonged co-administration of the two drugs is likely to result in reduced ibrutinib clearance and subsequent cardiotoxicity.

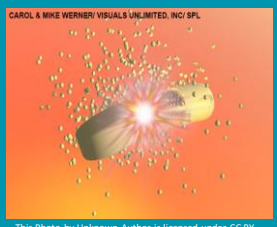
For patients who present with atrial fibrillation requiring rate control while taking ibrutinib, the recommended treatment sequence is:

- beta blockers (with optimisation of dosage as tolerated)
- digoxin if required (doses should be spaced 6 hours apart from ibrutinib to minimise potential for P-glycoprotein interactions in the gastrointestinal tract which may increase the blood levels and effects of digoxin).

If further rate control therapy is needed and diltiazem is prescribed, the dose of ibrutinib should be reduced by 50% to 75%, depending on the patient's clinical requirements.[1,2]

Conclusion

Medication review is essential for high-risk patients at every transition of care. This case highlights the need for clear guidelines with recommendations on cardiac assessments for high-risk patients and management of new onset cardiac toxicities.



Selected references

1. More L et al. Expert analysis: Ibrutinib-associated cardiotoxicity. Latest in cardiology 2020 Jan 21.
2. Stuhlinger MC et al. Recommendations for ibrutinib treatment in patients with atrial fibrillation and/or elevated cardiovascular risk. Wien Klin Wochenschr 2020;132:97-109.