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Are cardiovascular adverse events with Ibrutinib well considered?

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Background

- Chronic lymphocytic leukemia and mantle cell lymphoma have a new standard of care:
  - **Ibrutinib** (metabolized by CYP 3A4/5 and P-glycoprotein inhibitor)
- Cardiovascular (CV) adverse events are known with
  - **atrial fibrillation** (AF) (5-13,8%),
  - **bleeding event** (BE) (grade 3 or 4 about 3-4%)
  - **hypertension**
- CV pre-treatment evaluation is not required in Ibrutinib summary of product characteristics (SPC)

Objectives

❖Evaluate whether the CV risks are considered regarding the prescription of Ibrutinib

❖Measure cardiovascular adverse event occurrence during treatment

Material and Methods

A retrospective analyze was conducted including patients with Ibrutinib initiation in our hematology department from May 2014 to July 2017.
A database was constituted consulting all the medical records including:

- demographic, clinical and biological informations
- adverse events
- CV evaluation
- potential drug interactions

The incidence of AF and BE and the CHA_2DS_2-VASc score were calculated

Results

55 medical records were analyzed
The patient's mean age was 70 years old

Risk factors evaluation

65% had at least one CV risk factor
5 patients had more than 3 CV risk factor

38% had CV monitoring during their treatment

25% had at least one initial cardiac exam (ECG/Holter, echocardiography, cardiology consultation)

Other CV adverse events

✓ **One patient had myocardial infarction**

✓ **3 patients developped hypertension**

Atrial Fibrillation

✓ **4 patients developped AF 1 to 7 months after starting treatment**

41 patients had no one CV exam

AF was treated by anti-coagulant and anti-arrhythmic

One patient with CHA_2DS_2-VASc < 2 was treated whereas initiation threshold treatment is 2

Ibrutinib dose was decreased for 2 patients, maintained for one and stopped the fourth patient

No potential cause could be identified
These adverse events were described in Ibrutinib SPC

One patient had drug-drug interactions (Irbesartan)
Patients used a mean number of 5 drugs
> ¼ of patients used 7 or more medications

Bleeding events

✓ **24 patients had at least one BE**

One event grade 3 and 8 events grade 2

5 patients were under anti-platelet medication

4 patients had drug-drug interactions (Irbesartan, Verapamil, Voriconazole)

Discussion

Our results show that cardiac pre-treatment exam are few performed (25%) despite our patients CV risk factors

With 7,2% of AF, this risk is not negligible considering the limited cohort

Almost half (44%) of patients presented BE. A part of serious BE could have been prevented, as concomitant drugs, especially CYP 3A4 inhibitors, seems to play a role in CV adverse event occurrence. Patients are all the more exposed at BE because of their comorbidities can require anti-platelet medication.

Conclusion

The therapeutic management of adverse event seems to be not standardized.
As a result of drug interactions and CV consequence, which can lead to serious outcomes, a multidisciplinary consultation including hematologist, cardiologist and pharmacist should be established at the initiation and during treatment by Ibrutinib

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