Atrial fibrillation following initiation of Ibrutinib is an increasingly recognized phenomenon.

Ibrutinib has emerged as a widely used treatment option for patients with chronic lymphocytic leukemia (CLL), mantle cell lymphoma, and Waldenstrom’s macroglobulinemia, especially as salvage therapy for refractory disease.

Although the clinical relationship between atrial fibrillation and Ibrutinib is well known, there is very little investigation of the relationship between ventricular arrhythmias and initiation of Ibrutinib.

Atrial fibrillation often requires treatment without discontinuation of Ibrutinib, but in many cases ventricular arrhythmias can be fatal.

Data comparison between ventricular arrhythmias and Ibrutinib has shown inconsistent results in terms of both incidence and mortality.

Our clinical hypothesis is that Ibrutinib is associated with a much higher incidence of ventricular arrhythmias than patients not treated with Ibrutinib and the incidence will increase with longer duration of treatment with Ibrutinib.

An electronic database search was performed through MEDLINE/PUBMED, EMBASE, Thomson Reuters’ Web of Science, the Cochrane Library, Google Scholar, and Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov

Using standardized methods the following keywords were searched: “Ventricular Arrhythmia, Ventricular Tachycardia, Ibrutinib.”

We considered eligible all randomized controlled trials (RCTs) comparing Ibrutinib with any control group (placebo, no-treatment or standard care, non-pharmacological interventions or any active drug).

All RCTs were considered for inclusion irrespective of patients’ baseline conditions, background therapy, Ibrutinib dose, study follow-up or language of publication.

The primary outcomes were the incidence of ventricular arrhythmias and mortality from these ventricular arrhythmias.

For both outcomes we used a broad definition of the conditions.

Ventricular arrhythmias were defined as: sustained wide-complex monomorphic or polymorphic tachycardia with heart rate greater than 120 beats/min for at least 30 seconds or reported by investigators as an adverse event.

This systematic review and meta-analysis conducted by the principles set in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement.

Q statistic of Chi-square value test and I2 index (inconsistency index) were used to evaluate the heterogeneity of individual studies contributing to the pooled estimate.

RESULTS

In 3,809 patients being treated with Ibrutinib, the incidence of ventricular arrhythmias was almost 5-fold higher in patients being treated with Ibrutinib compared to patients on other treatment regimens

→ RR 4.82, 95% CI 2.22-10.45, p <0.0001

On meta-regression, when plotting log odds ratio of incidence of ventricular arrhythmias (y-axis) against duration of therapy (x-axis), incidence increased further with longer duration of treatment (coefficient = 0.344, p=0.0001).

CONCLUSION

For patients treated with Ibrutinib, there was a markedly higher rate of ventricular arrhythmias compared to patients on all other treatment regimens.

Currently, there are no evidence-based guidelines regarding the utility and method of surveillance, choice between pharmacological treatment or interventional therapy, and the safety and efficacy of regarding Ibrutinib cessation for ventricular tachycardias.

Meta-regression showed a trend towards increased incidence of ventricular arrhythmias with longer duration of treatment reached statistical significance.

There needs to be more surveillance for ventricular arrhythmias, and it should be considered a potential major side effect, which can increase morbidity and mortality, for patients initiating Ibrutinib.

REFERENCES

DISCLOSURES: NONE