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Perspective

A Retrospective Analysis of Ibrutinib-Associated Pneumonia

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Tyrosine kinase inhibitors and their modulation of cancer cell proliferation may be associated with various adverse events serious enough to consider a change in therapy. Specifically, pneumonia rates among patients with cancer have been rising steadily for the last decade, perhaps due to increased use of stronger, sometimes immune modulating drugs such as ibrutinib. This particular agent targets Bruton's tyrosine kinase, which is expressed most prominently in B cells, the cell from which most non-Hodgkin's lymphomas and chronic lymphocytic leukemia originate.

The FDA has a publically available database that contains all adverse event reports from consumers, medwatch, and drug companies. This database is known as the FDA Adverse Event Reporting System (FAERS) and it contains over 10 million reports of adverse events that have been de-identified for safety of the patients reporting the adverse events. A subset of data from this database will look at the incidence rate of pneumonia in patients who took ibrutinib for mantle cell lymphoma, B-cell leukemia, and non-hodgkin's lymphoma from 2010 through 2015. The incidence rate of pneumonia in ibrutinib will be compared to all other tyrosine kinase inhibitors to determine whether there is a significant increase of pneumonia incidence in ibrutinib compared to other tyrosine kinase inhibitors. A proportional t-test ($p < 0.05$) will be used to determine significance.

All reports of ibrutinib from 2010 through 2015 was extracted from the database. Indications for the drug ranged from mantle cell lymphoma, b cell leukemia, and non-hodgkin's lymphoma, which was analyzed through subgroup analysis as part of our secondary endpoints. Subsequently, pneumonia was mined from the database in order to determine the incidence of pneumonia. This process was duplicated for all other tyrosine kinase inhibitors and the ratios of each of them was compared to ibrutinib. Our null hypothesis states that there is no difference between the incidence rates of pneumonia in ibrutinib-associated reports compared to all other tyrosine kinase inhibitors, which we were able to reject and accept the alternative hypothesis that ibrutinib-associated pneumonia incidence is statistically significantly greater than the incidence rate of pneumonia in all non-ibrutinib reports during this period.

Limitations of this study include the retrospective nature and lack of supporting content for each reported reaction, such as lab values, progress notes, or physician oversight of any kind. Also, only serious adverse events are reported to the database and therefore underreporting is prevalent in these types of studies. Ideally, future studies would correlate not only ibrutinib use as well as demographic trends but all-cause mortality as evaluated through a Kaplan-Meier curve, testing against each disease state.

Overall assertions pertaining to overall survival are limited given the retrospective case-control nature of this study and the tendency for confounding variables to influence a study such as this. Nonetheless, the rate of pneumonia was 33% lower during this period in non-ibrutinib reports than with ibrutinib-associated events.

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