LymphomaHub

CLL/SLL

Ibrutinib monotherapy shown to result in increased susceptibility of PCP opportunistic infections

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Ahn I.E., from the Medical Oncology Service, National Cancer Institute, and Jerussi T., from the National Institutes of Health, and colleagues, recently published an interesting finding from two prospective studies of 96 patients with CLL, published in Blood, October 2016. The authors reported the incidence rates of patients being treated with ibrutinib developing Pneumocystis jirovecii pneumonia (PCP). PCP is an opportunistic fungal disease typically seen in immunocompromised individuals such as patients with AIDS.

Highlights:

- PCP incidence was detected by PCR following respiratory symptoms or abnormal CT
- Patients developing PCP had $CD4^+$ T-cell count >500/μL, IgG >500 mg/dL
- Incidence of PCP during ibrutinib monotherapy estimated as 4.5% (1 year) and 5.6% (2 years)
- All PCP events successfully resolved with oral therapy
- Clinicians prescribing BCR pathway inhibitors may need to be mindful of the PCP risk

In an accompanying commentary, Zent C.S., from the University of Rochester Medical Center, mentions that the FDA and EMA both warn that the PI3Kδ inhibitor idelalisib, another BCR pathway inhibitor, increases the risk of PCP and other opportunistic infections when used in patients with progressive CLL.

Conclusion:

The absence of reduced $CD4^+$ T-cell counts or IgG levels in CLL patients developing PCP while on ibrutinib monotherapy suggests another mechanism linked to BTK inhibition may be the cause. Further studies will need to be done to confirm the link between BCR pathway inhibitors in the treatment of CLL and the incidence of opportunistic infections, such as PCP.

Abstract:

Atypical Pneumocystis jirovecii pneumonia in previously untreated patients with CLL on single-agent ibrutinib.

Ibrutinib is not known to confer risk for Pneumocystis jirovecii pneumonia (PCP). We observed 5 cases of PCP in 96 patients receiving single-agent ibrutinib, including 4 previously untreated. Clinical presentations included asymptomatic pulmonary infiltrates, chronic cough, and shortness of breath. The diagnosis was often delayed. Median time from starting ibrutinib to occurrence of PCP was 6 months (range, 2-24). The estimated incidence of PCP was 2.05 cases per 100 patient-years (95% confidence interval, 0.67-4.79). At the time of PCP, all patients had CD4 T-cell count >500/μL (median, 966/μL) and immunoglobulin G (IgG) >500 mg/dL (median, 727 mg/dL). All patients underwent bronchoalveolar lavage. P jirovecii was identified by polymerase chain reaction in all 5 cases; direct fluorescence antibody staining was positive in 1. All events were grade ≤2 and resolved with oral therapy. Secondary prophylaxis was not given to 3 patients; after 61

patient-months of follow up, no recurrence occurred. Lack of correlation with CD4 count and IgG level suggests that susceptibility to PCP may be linked to Bruton tyrosine kinase (BTK) inhibition. If confirmed, this association could result in significant changes in surveillance and/or prophylaxis, possibly extending to other BTK inhibitors.

References:

1. Ahn I.E., Jerussi T. *et al*. Atypical Pneumocystis jirovecii pneumonia in previously untreated patients with CLL on single-agent ibrutinib. Blood. Oct 2016. 128:1940-1943; doi:10.118.
2. Zent C.S. CLL: an acquired immunodeficiency disease. Blood. Oct 2016. 128:1908-1909; doi:10.1182.