

Bruton tyrosine kinase inhibitors (BTKi) therapies in chronic lymphocytic leukemia (CLL): Review of multiple trials data for incidence of lymphocytosis and designation of partial response with lymphocytosis (PRL).

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Abstract

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Background: In trials with BTKi, lymphocytosis alone may not be a sign of progression but rather treatment related redistribution of lymphocytes from tissues into the peripheral blood (Cheson et al 2012). This observation was later incorporated in iwCLL 2018 criteria. However, no clear details were provided on how to assess lymphocytosis along with other parameters to derive an overall timepoint response (OTR) in a clinical trial setting. While PRL is a response category used to assess lymphocytosis in many clinical trials, it has not been defined in iwCLL 2018. Furthermore, iwCLL 2018 defines Absolute Lymphocyte Count (ALC) progression (PD) as an increase of ALC $\geq$ 50% compared to baseline whereas conventionally progression is defined in comparison to nadir, which may lead to under reporting of ALC PD. **Methods:** Data from multiple (8) phase II/III CLL trials with BTKi (frontline and relapsed/refractory setting), were retrospectively analyzed. Subjects with a post baseline (post-BL) timepoint (TP) were analyzed for the incidence of ALC PD and an OTR designation of PRL, PD and other non-PD assessments (Stable Disease (SD), Non-PD and Unknown (UNK)). **Results:** We identified 1976 subjects with a total of 17134 post BL TPs. There were 1182 TPs (6%) with ALC PD. Out of these TPs with ALC PD, 497 TPs had OTR of PRL (42% TPs with ALC PD), 365 TPs (31%) were assessed as non-PD and 320 (27%) TPs were assessed as PD. 104 TPs (33%) of subjects with OTR of PD had at least one additional parameter driving PD. Thus, ALC PD is a common occurrence with BTKi and in line with the Cheson 2012 guidance, ALC PD alone should not be considered as overall progression. We propose that initial ALC PD with BTKi should not be considered a sign of progression but rather a treatment effect and should be assessed as PRL. However, PRL should only be assessed if Partial Response (PR) is achieved in at least 2 other involved iwCLL group A parameters (nodes, liver or spleen) and 1 group B parameter (hemoglobin or platelets). An initial decrease/normalization of the ALC compared to baseline with a subsequent progression compared to nadir, may be considered true progression in a setting of continued BTKi. If only one other group A parameter is involved and is PR with associated ALC PD, SD may be a more appropriate overall response than PRL. **Conclusions:** ALC PD and PRL are common in BTKi, but there is a need for standardization of the definition of ALC PD and its role in determination of OTR of PRL. We propose that ALC PD should be assessed by comparing ALC with nadir and not baseline. If PRL is assigned only when PR is met by other criteria along with ALC PD, PRL could be a part of determining Overall response rate (ORR) in protocols.

Future prospective studies are needed to estimate the true incidence of ALC PD and its impact on ORR with BTKi as well as other agents which induce lymphocytosis.

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