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Opinion Article

Importance of Prolymphocytes in Patients with Chronic Lymphocytic Leukemia Receiving BTK Inhibitor Treatment

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DESCRIPTION

The most prevalent type of leukemia in western nations is called Chronic Lymphocytic Leukemia (CLL), which is defined by monoclonal proliferation of CD5+ B cells that appear in blood, marrow, and lymphoid tissues. As of right now, CLL is still largely incurable and has a variable clinical course, with some patients developing the disease quickly within months and others showing a relatively slow course and needing to be monitored for years. Numerous indicators have been linked to the clinical course of CLL, including laboratory biomarkers and clinical parameters. In clinical practice, a prognostic model called CLL-IPI is commonly used to stratify patients with CLL. It combines five traditional parameters: age, clinical stage, β2-Microglobulin (β2-MG), Immunoglobulin Heavy-Chain Variable region gene (IGHV) mutation status, and *TP53* status. Patients with CLL often have tiny, microscopic lymphocytes in their peripheral blood, with clumped chromatin and little cytoplasm. There are always smudge or basket cells present, and in CLL patients, a higher proportion of smudge cells is linked to a longer survival time. Some CLL patient smears show varying proportions of prolymphocytes, which are nuclei with large, predominant nucleoli in association with moderately clumped chromatin.

Research has been done on the effect of prolymphocytes on prognosis in CLL patients. Numerous studies have demonstrated that higher prolymphocyte counts, both in terms of percentage and absolute number, are associated with poorer survival outcomes and resistance to conventional therapies. In the Chronic Lymphocytic Leukaemia Trial 4 (LRF CLL4 trial), they assessed the impact of prolymphocytes in 777 patients. The higher prolymphocyte counts were linked to indicators of a poor prognosis, such as advanced stage and cytogenetic abnormalities, and that these markers also predicted a shorter Progression Free Survival (PFS) and Overall Survival (OS). The optimal threshold for classifying elevated prolymphocytes in CLL risk stratification has not yet been determined, though. Furthermore, research on prolymphocyte's prognostic significance that is currently available dates back to the days before the novel therapies. The therapeutic landscape for CLL has altered due to the introduction of novel agents, which have also significantly improved patient prognoses. Thus, more research is needed to determine the prognostic significance of prolymphocytes in CLL patients receiving novel agent treatment. In this study, peripheral blood smears from CLL patients who were not receiving treatment were examined in retrospect. The study determines the ideal cutoff for the percentage of prolymphocytes that was used as a prognostic marker and examined the effect of the increased prolymphocytes on Treatment Free Survival (TFS), which is less likely to be influenced by treatment therapies and OS in patients with CLL.

First, we investigated the prognostic significance of increased prolymphocytes for PFS in the novel agent era. The study also analyzed the association of increased prolymphocytes with other classical prognostic factors. Less people in China have CLL, a form of leukemia that is common in western nations. The disease's clinical trajectory is highly variable. Therefore, it's important to identify more trustworthy prognostic markers. There has been a great deal of research on cytogenetic and molecular biomarkers, but not as much on the morphological characteristics of CLL cells and their prognostic significance.

According to our research, patient outcomes are correlated with the proportion of prolymphocytes in peripheral blood among patients with CLL, which is a crucial and clinically viable marker. 1% was the ideal prolymphocyte percentage cutoff value determined by X-tile analysis. Patients whose peripheral blood prolymphocyte count was greater than 1% showed significantly shorter survival times and worse overall survival rates. Next, a multivariate analysis was carried out, which included five factors related to prolymphocyte percentage and CLL-IPI.

Prolymphocyte percentage >1% did not demonstrate an independent prognostic effect on OS, but it did demonstrate a marginally independent prognostic effect on TFS (P=0.071). Further examination verified that patients exhibiting prolymphocyte percentages >1% and ≤1% demonstrated statistically significant variations in traditional prognostic indicators, such as the presence of *TP53* mutations and *IGHV* mutations.

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