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Secondary autoimmune cytopenias in chronic lymphocytic leukemia

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ABSTRACT

Secondary autoimmune cytopenias in chronic lymphocytic leukemia are distinct clinical entities that require specific management. These autoimmune disorders have a complex pathogenesis that involves both the leukemic cells and the immune environment in which they exist. The mechanism is not the same in all cases, and to varying degrees involves the chronic lymphocytic leukemia (CLL) cells in antibody production, antigen presentation, and stimulation of T cells and bystander polyclonal B cells. Diagnosis of autoimmune cytopenias can be challenging as it is difficult to differentiate between autoimmunity and bone marrow failure due to disease progression. There is a need to distinguish these causes, as prognosis and treatment are not the same. Evidence regarding treatment of secondary autoimmune cytopenias is limited, but many effective options exist and treatment can be selected with severity of disease and patient factors in mind. With new agents to treat CLL coming into widespread clinical use, it will be important to understand how these will change the natural history and treatment of autoimmune cytopenias.

1. Background and clinical experience

The course of chronic lymphocytic leukemia (CLL) is frequently complicated by concomitant autoimmune cytopenias (AIC). The most common of these secondary AIC is autoimmune hemolytic anemia (AIHA), which is an antibody-mediated destruction of autologous red blood cells (RBCs). Second most common is immune thrombocytopenia (ITP), which shares some features with AIHA and has a similar mechanism targeting platelets. These two syndromes may occur in isolation, sequentially in the same patient, or present in combination as Evan's syndrome. Pure red cell aplasia (PRCA) and autoimmune granulocytopenia (AIG) are comparatively rare and can occur alone or in combination with other AIC. PRCA can present with anemia as in AIHA, but involves a virtual absence of red cell precursors due to immune destruction of erythrocyte progenitor cells and no hemolysis. AIG has a similar mechanism to PRCA in which myeloid precursors are destroyed and patients develop infections.

1.1. Incidence

While other autoimmune disorders have been reported in CLL, AIC are by far the most frequent immune complication [1,2]. Figures regarding the percentage of patients affected by secondary AIC vary. Exact numbers are difficult to ascertain as AIC can present at any time in the CLL disease course, including predating CLL diagnosis. Further complicating the issue, the rate in any given cohort will vary based on the cohort composition as AIC are associated with higher Rai stage, prior cytotoxic treatment, and more aggressive disease characteristics [3,4]. For example, heavily pretreated cohorts will have a higher incidence of AIC compared to populations enriched with asymptomatic, treatment-naïve patients. The retrospective nature of studies reporting incidence also limits their accuracy as not all patients underwent rigorous diagnostic testing for cytopenia diagnosis and some may have had cytopenias from alternate causes such as bone marrow infiltration with leukemia.

Despite these challenges, a reasonable estimate is that AIC occur in 4%–10% of CLL patients with the highest reported rates coming from analysis of therapeutic clinical trials and lower estimates coming from large institutional studies [1,3–8]. This is a significant number of patients, as CLL is the most common adult leukemia with an incidence rate of 3.83 cases per 100,000 person-years. It is even more prevalent due to the long survival of CLL patients, making complicating AIC an important matter [9,10].

Relative frequency of the types of AIC is similar in nearly all reported cohorts with AIHA being the most common at 55%–70% of patients with AIC, ITP the second most common at 18%–47%, and PCRA and AIG being decidedly less common at 12% and 4%, respectively [1,3–8]. Patients prone to AIC may also develop more

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