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Double productive immunoglobulin sequence rearrangements in patients with chronic lymphocytic leukemia

Carlo Visco, Francesca Moretta, Erika Falisi, Monica Facco, Francesco Maura, Elisabetta Novella, Ilaria Nichele, Silvia Finotto, Ilaria Giaretta, Elisa Ave, Omar Perbellini, Nicola Guercini, Maria Teresa Scupoli, Livio Trentin, Valentina Trimarco, Antonino Neri, Gianpietro Semenzato, Francesco Rodeghiero, Giovanni Pizzolo, Achille Ambrosetti

Abstract

The immunoglobulin heavy chain variable (IGHV) gene mutational status represents a major prognostic marker in chronic lymphocytic leukemia (CLL). Usually, the prognostic implications of IGHV gene analysis can be reliably ascertained but, occasionally, double productive rearrangements have been detected. Clinical presentation and biological features of such cases are unknown. Sixty patients with morphologically and phenotypically monoclonal CLL but double productive IGHV rearrangements were retrospectively identified by mRNA analysis from three Hematology Institutions. Clinical and biological features and survival of these 60 patients were compared with a control group of patients with CLL and single IGHV rearrangement. A prospective registry was used to assess the epidemiology of double productive IGHV among incidental patients with CLL. Using standard criteria to define IGHV-mutated (M) or unmutated (U) cases, 39 of the 60 patients (65%) with double productive IGHV rearrangement had concordant status (23 MM, 16 UU), while 21 (35%) had discordant IGHV status. As compared with M patients, the MM ones had lower CD38 expression, more favorable cytogenetics and more indolent clinical behavior. Cases with UU had similar characteristics of U patients. Discordant cases presented with adverse prognostic features and had an aggressive clinical behavior requiring early treatment, similar to U patients. The prevalence of double IGHV was 3.1%. Patients with CLL with double concordant mutational status (MM or UU) have a clinical course similar to that of the corresponding single IGHV status, while those exhibiting discordant status represent a high risk population. This may help correct stratification within clinical trials.