Associated cancers in Waldenstrom Macroglobulinemia: clues for common genetic predisposition

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Several population-based and cohort studies have reported an increased overall risk of second cancers in lymphoproliferative disorders (LPD). Most of these studies showed an increased risk of MDS/AML and found an association with exposure to alkylating agents or nucleoside analogues. The development of second solid cancers in LPD, however, is still a controversial issue and is object of speculation. Genetic predisposition, exposure to some environmental factors, and the immune dysfunction typical of LPD, have all been considered as contributing factors. Furthermore, an apparent increased risk of second cancers could be due to a "surveillance effect", that is a higher detection rate of primary cancer during follow-up or the result of the improvement of long-term survival achieved with therapeutic advances in patients with LPD.

To assess the frequency, characteristics and predictive factors of second cancers in Waldenstrom Macroglobulinemia (WM) and to evaluate whether WM patients are at higher risk of second cancers as compared with an age and sex-matched control population of the same geographical region, we performed a retrospective study on 230 WM patients with a median follow-up from diagnosis of 5.6 years (0.5-29.3). Twenty-four patients (10.4%) developed solid cancers and 11 (4.8%) second hematologic malignancies with a median time from diagnosis of 4.4 and 4.1 years, respectively.

In a competing risk model, the cumulative incidence of solid cancers was 7% at 5 yrs, 12% at 10 yrs, 18% at 15 yrs, while the incidence of hematologic malignancies was 4% at 5 yrs, 7% at 10 yrs, 9% at 15 yrs. The overall risk of second cancer was 1.7 times higher than expected (P=0.002). WM patients were at increased risk for diffuse large B-cell lymphoma [standardized incidence ratio (SIR) 8.64 $P<0.0001$], MDS/AML (SIR 9.5 $P<0.0001$), brain cancer (SIR 7.59 $P<0.0007$). In conclusion, WM patients proved to be at higher risk of second cancers as compared to the general population. The excess of risk was mostly due to hematologic malignancies and brain cancers. The risk of hematologic malignancies was almost 4 fold higher in previously treated patients.

Based on the evidence of genetic factors and familial predisposition in WM patients, the evaluation of the risk of other cancers among WM patients and their kin may furnish an important information for common genetic risks of

cancer. Recently, Hanzis et al. (*Clinical Lymphoma, Myeloma & Leukemia, 2011*) evaluated the risk of associated cancers in 924 WM patients and their kin. This study identified specific cancer associations with WM. Familial WM subgroup analysis showed a higher incidence of prostate cancer ($P = .046$) in sporadic WM patients, while patients with familial WM had a higher incidence of lung cancer ($P = .0043$). The kin of patients with familial WM presenting other B-cell disorders in their family members showed an increased number of myeloid leukemic events ($P < .0001$) suggesting the presence of a common hematopoietic stem cell defect in these patients. These results indicate that WM patients have a higher incidence of associated malignancies, with specific cancer clustering based on the familial predisposition to WM.