W16: Genetic analysis of Diffuse Large B-cell Lymphoma occurring in cases with antecedent Waldenström Macroglobulinaemia reveals different patterns of clonal evolution.

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Diffuse large B-cell lymphoma (DLBCL) occurs in 2-10% of cases with antecedent Waldenström Macroglobulinaemia (WM). It is generally presumed that DLBCL arises from the WM clone. However, this is not conclusively established. Given the lack of understanding of the clonal relationship between the two lymphomas, we aimed to use easily applicable genetic analyses on paired samples to determine whether DLBCL arises from the WM clone or as a de-novo lymphoma.

We extracted DNA from and performed MYD88 L265P and immunoglobulin heavy chain (IgHv) PCR and sequencing on WM and subsequent DLBCL samples of 4 patients (all males). Their mean age was 71 years (range 61-89 years). Patient 1 received Chlorambucil and prednisolone for WM followed by Ibrutinib and Rituximab at relapse, patient 2 received Dexamethasone and Rituximab, patient 3 was treatment naïve at the time of diagnosis of DLBCL and patient 4 received Fludarabine and Cyclophosphamide. Patient 1 was on Ibrutinib at the time of diagnosis of DLBCL.

The average time to transformation was 4.1 years (range 1.5-9), and patients were treated with high dose chemoimmunotherapy protocols +/- autologous stem cell transplantation and/or CNS prophylaxis with high dose methotrexate.

WM was in partial remission in cases 1-3 and in complete remission in case 4 at the time of transformation. The site of disease was extranodal in 3 of the 4 cases including the brain in case 1. Cell of origin was activated B cell subtype (ABC) in cases 1 and 2 and germinal centre (GC) subtype in cases 3 and 4.

The minimal amount of brain tissue on Patient 1 was subjected to laser-capture microdissection, IgHv PCR and cloning before sequencing.

MYD88 L265P mutation was detected in all 4 cases at WM diagnosis, and in 3 cases at occurrence of DLBCL. Patient 3 with wtMYD88 DLBCL had variable IgHv to the treatment naïve WM, indicating independent clonal origin. Patients 2 and 4 had the same IgHV, indicating clonal evolution from the antecedent WM. IgHv on patient 1 was inconclusive despite laser microdissection.

IgHv and MYD88 mutation analysis from archived bone marrow and secondary lymphoma tissue can help determine if the DLBCL has arisen from the original WM clone or is a de-novo lymphoma. We demonstrate in our case series that both scenarios can occur. This

information is important for prognosis as de-novo DLBCL has a better prognosis than transformed lymphoma.

Furthermore, we present the first reported case of ABC DLBCL occurring in the CNS in a patient with WM while on active treatment with Ibrutinib (case 1). The transformation occurred in a patient who was MYD88 L265P mutation positive, both at diagnosis of WM and subsequent DLBCL. Ibrutinib is effective both in WM and in DLBCL, particularly if it is of the ABC subtype and is reported to penetrate the CNS, which makes the transformation to DLBCL while on the drug an unusual feature.