Improving Precision in Prognostication for the Elderly Population with Follicular Lymphoma

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profiling studies have provided significant insight into the genetic diversity of FL. Data emerging from these studies reveal that alterations in genes largely involved in epigenetic regulation and modification of chromatin dominate the FL mutational landscape [7].

Morin sequenced tumours and matched normal DNA from non-Hodgkin Lymphoma patients in 117 samples and 10 cell lines. Histone methyl transferase MLL2 was found to be most frequently occurring and found in 89% of FL [8]. MLL2 is a tumour suppressor gene in Diffuse Large B cell Lymphoma (DLBCL) and FL. Inactivating mutations are thought to be drivers of FL tumorigenesis.

Other important epigenetic modifiers in FL include mono allelic and inactivating mutations in histone linker ARID1A which helps regulate DNA repair and is identified in approximately 11% of FL [9].

With the combination of molecular markers, m7-FLIPI emerged from a retrospective analysis that reviewed two cohort studies-the German Low-Grade Lymphoma Study Group and a validation cohort group from the British Columbia Cancer Agency (BCCA) of patients treated with Rituximab-cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine and prednisone (R-CHOP).

The inclusion criteria were patients with grade 1-3a FL, with symptomatic advanced stage disease requiring therapy based on FLIPI score. The retrospective study analyzed the coding sequences of 74 genes with established recurrent mutations in FL and correlated with the FLIPI score. This was in turn named the m7-FLIPI score.

The m7-FLIPI score included a high-risk FLIPI score, poor Eastern Cooperative Oncology Group (ECOG) performance status, and non-silent mutations in 7 genes known to be deregulated by FL, validated in the BCCA cohort. The 7 genes were *ZH2*, *ARID1A*, *MEF2B*, *EP300*,

4	FDG uptake moderately increased compared to the liver	PR/SD/PD
5	FDG uptake markedly increased compared to the liver and/or new sites of disease	
Note: *Response to treatments defined by the Lugano classification. CR: Complete metabolic Response; PR: Partial metabolic Response; SD: Stable Disease; PD, Progressive Disease.		

Prompt identification of patients with transformed follicular lymphoma is needed. Several attempts have been made to correlate the histology FL grade encompass and FL transformation with the intensity of FDG uptake in PET/CT.

End-of-treatment PET scan had been compared to minimal residual disease detection by molecular biology in predicting long term outcomes in FL. PET CT scan was able to image FL independently from heterogeneity of neoplastic clones which could be missed by molecular techniques.

Novelli in a longitudinal study observational study performed on 16 FL and 5 DLBCL patients for 3.5 years. These groups of patients had under-gone PET-guided biopsy in the hottest FDG uptake site and were able to demonstrate a close correlation between the histologic grade and SUV max detected on a biopsied node [17].

While radiological techniques proved to be important incorporation into the prognostication system, there were limitations with FDG PET/CT scans as well. FDG PET/CT had nonspecific uptake in inflammatory or infectious lesions. Variable physiological uptakes in normal tissues or organs could be confused with malignancy.

Fortunately, there were new studies that aimed to overcome PET limitations with vectors or ligands that could specifically target cell-surface markers. Phenotypic PET imaging was a promising alternative approach to obtain a specific non-invasive characterization of malignancies by whole-body imaging [18].

Follicular lymphoma is the most common indolent non-Hodgkin lymphoma, typically affects older adults, whose median age at diagnosis is 65 years [19].

FL is considered as an indolent but incurable disease with a median life expectancy of approximately ten years.

New clinical and biological prognostic factors are needed, to tailor therapy better, above all in elderly patients not eligible for aggressive chemotherapy.

While the use of FDG PET/CT imaging and molecular

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