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Improving Precision in Prognostication for the Elderly Population with Follicular Lymphoma

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Abstract

Follicular Lymphoma (FL) remains a highly heterogeneous entity with various outcomes. In some patients, the disease exhibits aggressive and chemotherapy-resistant behavior. On the other hand, the disease remains indolent with durable remissions after initial treatment.

Such complexity in risk-stratifying patients is more so important in elderly patients with FL where early detection of the progression of the disease can lead to early treatment and prolongation of the quality of life.

Several studies suggest that disease recurrence within 2 years of first-line treatment of FL occurs consistently in as many as 20% of patients independent of maintenance rituximab.

Keywords: Positron Emission Tomography Computer Tomography; Chemotherapy; Follicular Lymphoma; Quality of life

Introduction

This review article aims to highlight the importance of incorporating accurate and precise prognostic markers including molecular markers and radiological techniques such as Positron Emission Tomography Computer Tomography (PET CT) scan into the scoring system. More importantly, these markers can be targeted at the elderly population with FL who require more frequent follow-up or early initiation of treatment.

With the heterogeneity of FL, we know that clinical indices of risk have already been created to identify patients with more aggressive diseases and shorter responses to treatment. These include the Follicular Lymphoma International Prognostic Index (FLIPI) and the FLIPI 2 scores [1,2].

Conventionally, the treatment depends on the stage of the disease so initial staging should be thorough, particularly in the small proportion of patients with localized stage I and II. The staging is performed according to the Ann Arbor classification system [3].

Staging typically includes a CT scan, bone marrow aspirate and biopsy with complete blood test including chemistry and screening for HIV, HCV and HBV must be done at baseline.

Prognostic indices are then necessary to guide physician's decision-making process. As result of international cooperation, the FL International Prognostic Index (FLIPI) was established in 2004 [4].

However, the FLIPI was born before rituximab era and was based on retrospective data, so a revised FLIPI 2 (incorporating beta2 macroglobulin, the diameter of largest lymph node, bone marrow involvement, and hemoglobin level) was introduced [5].

The watchful waiting approach typically applies in a low tumour burden or asymptomatic patient or in most cases where treatment is halted in view of treatment related toxicity.

However, the clinical approach to elderly patients is a complex issue and hence age should not be a hindrance to closer monitoring or initiation of treatment.

The elderly population shows alteration in tumour-host biology and difference in both cellular and humoral mediated immune response.

Besides a complete evaluation of the elderly patient including use of comprehensive Geriatric Assessment (GCA), this article aims to review precise markers which can prognosticate early disease progression requiring treatment. With more precise prognosticator markers, this dismisses the conventional watchful and waiting approach which the elderly population is easily labeled under in view of age.

Review of Literature

The use of molecular markers for prognostication

Yet, beyond the clinical realm, biologic predictors of risk in FL involved mutations in key genes, modification of histones, and changes in the FL tumoral microenvironment [6]. These biologic contributors of FL risk have not been incorporated into clinical use. Furthermore, the FL could biologically be more complex and aggressive in the elderly population.

Casulo investigated clinical prognostic indices in FL and reviewed novel prognostic markers predicting poor risk. Large-scale genomic-wide

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*, *FOXO1*, *CREBBP*, and *CARD11*.

The retrospective study proceeded to identify high and low-risk groups of patients more robustly than the FLIPI score alone. In conclusion, the m7-FLIPI prospectively identifies the smallest subgroup of patients (28% and 22% respectively) at the highest risk of early failure of first line immunochemotherapy and death. This indicated that the m7-FLIPI might also be useful in the up-front identification of low-risk patients with the excellent outcome with currently applied immunochemotherapy regimens, and a subset might qualify for treatment de-escalation strategies [10].

With the implementation of more accurate prognosticator markers, a de-escalation strategy could then be primarily targeted at the elderly population. These elderly populations would be able to undergo lower intensity chemotherapy with fewer side effects yet gain improvement in terms of progression-free survival.

All in all, the above clinical-genetic risk model could incorporate molecular data into a clinical prognostic index. Such a novel scoring system could also be used as predictive biomarker in future clinical trials.

FDG PET CT scan and detection of relapse

Moving on, apart from molecular markers, the use of radiological techniques including Positron Emission Tomography (PET) scans for follow-ups and early detection had also been of great interest in the FL population. PET scans could not only be used for disease staging or post-therapy evaluation but also guided therapeutic strategies specifically for elderly patients with FL who might benefit from early initiation of treatment.

Studies had shown that Flurodeoxyglucose FDG PET/CT detected more lesions than conventional CT scans, especially in terms of lymph node and extra-nodal involvement. FDG PET had a high potential to detect bone marrow involvement in high grade malignant lymphoma but also had low sensitivity for detection of diffuse bone marrow infiltration in low grade Non-Hodgkin Lymphoma (NHL) especially FL [11].

Le Dortz reported that 11% of patients considered early stage (I/II) FL following standard evaluation including physical examination, CT, and bone marrow biopsy were found to be having advanced III/IV stage when FDG PET/CT was considered [12]. This aspect appeared influential in choosing an optimal initial therapeutic strategy. This created a paradigm shift for modern FL management specifically targeting the elderly population.

The formal indication of PET used in FL came from the recently published Lugano recommendations for FDG-PET scan use for lymphoma staging and restaging. Lugano's recommendations stated that functional imaging with FDG-PET was the diagnostic standard tool for tumour burden assessment and treatment response evaluation in several FDG-avid lymphomas, including FL [13].

The presence of histologic transformation implied prognosis and first line therapy. Early reports of PET imaging in NHL noted higher Standard Uptake Value (SUVs) in aggressive NHL than in indolent forms [14]. This once again highlighted the potential for PET-CT to identify FL subsets at high risk of relapse following a rituximab containing chemotherapy in the post-treatment phase.

Analyses of FL patients enrolled in the PRIMA and FOLL05 trials, who had PET performed off-trial and interpreted locally within 3 months of completing therapy, found that a positive post-treatment PET scan was seen in about 25% of patients and predicted poor Progression-Free Survival (PFS) [1,15].

Furthermore, the Deauville scale was then invented and undertaken where a cutoff of 3 or lower was defined as a negative PET scan.

Score	Criteria	Interpretation*
1	No FDG uptake	CR
2	FDG uptake lower than or equal to the mediastinal blood pool	
3	FDG uptake higher than the mediastinal blood pool but lower or equal to liver	

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.		

Table 1: Deauville score showing a five-point scale for therapy stratification in patients with FDG-avid lymphomas [16].

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 markers remains invalidated in the current management of FL, recent publications have suggested benefits in numerous situations.

Hence, perhaps when we next review an elderly patient presenting with localized Follicular lymphoma, the patient will be further screened for molecular markers which have been identified to be aggressive in terms of histologic transformation. The patient will also undergo a pre- and post-treatment evaluation with an FDG PET CT scan.

Conclusion

In summary, FL can no longer be approached as a one-size-fits-all disease. The emergence of radiological and biologic prognostic biomarkers is revealing the extent of the heterogeneity of FL. Hence, we must aim to improve the current prognostication scoring system, especially for elderly FL patients. The use of radiation and biological means instead of a watch and wait approach might be more reasonable and effective.

Conflict of Interest

The authors have nothing to disclose.

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