A gene-expression profiling score for prediction of outcome in patients with follicular lymphoma: a retrospective training and validation analysis in three international cohorts


Summary

Background Patients with follicular lymphoma have heterogeneous outcomes. Predictor models to distinguish, at diagnosis, between patients at high and low risk of progression are needed. The objective of this study was to use gene-expression profiling data to build and validate a predictive model of outcome for patients treated in the rituximab era.

Methods A training set of fresh-frozen tumour biopsies was prospectively obtained from 160 untreated patients with high-tumour-burden follicular lymphoma enrolled in the phase 3 randomised PRIMA trial, in which rituximab maintenance was evaluated after rituximab plus chemotherapy induction (median follow-up 6·6–7·0 years [IQR 6–7]). RNA of sufficient quality was obtained for 149 of 160 cases, and Affymetrix U133 Plus 2.0 microarrays were used for gene-expression profiling. We did a multivariate Cox regression analysis to identify genes with expression levels associated with progression-free survival independently of maintenance treatment in a subgroup of 134 randomised patients. Expression levels from 95 curated genes were then determined by digital expression profiling (NanoString technology) in 53 formalin-fixed paraffin-embedded samples of the training set to compare the technical reproducibility of expression levels for each gene between technologies. Genes with high correlation (>0·75) were included in an L2-penalised Cox model adjusted on rituximab maintenance to build a predictive score for progression-free survival. The model was validated using NanoString technology to digitally quantify gene expression in 488 formalin-fixed, paraffin-embedded samples from three independent international patient cohorts from the PRIMA trial (n=178; distinct from the training cohort), the University of Iowa/Mayo Clinic Lymphoma SPORE project (n=201), and the Barcelona Hospital Clinic (n=109). All tissue samples consisted of pretreatment diagnostic biopsies and were confirmed as follicular lymphoma grade 1–3a. The patients were all treated with regimens containing rituximab and chemotherapy, possibly followed by either rituximab maintenance or ibrutinomab–tiuxetan consolidation. We determined an optimum threshold on the score to predict patients at low risk and high risk of progression. The model, including the multigene score and the threshold, was initially evaluated in the three validation cohorts separately. We determined optimal cut-offs and specificity of the score for the prediction of the risk of lymphoma progression at 2 years were assessed on the combined validation cohorts.

Findings In the training cohort, the expression levels of 395 genes were associated with a risk of progression. 23 genes reflecting both B-cell biology and tumour microenvironment with correlation coefficients greater than 0·75 between the two technologies and sample types were retained to build a predictive model that identified a population at an increased risk of progression (p=0·0001). In a multivariate Cox model for progression-free survival adjusted on rituximab maintenance treatment and Follicular Lymphoma International Prognostic Index 1 (FLIPI-1) score, this predictor independently predicted progression (adjusted hazard ratio [aHR] of the high-risk group compared with the low-risk group 3·68, 95% CI 2·19–6·17 [p=0·0001]). The 5-year progression-free survival was 26% (95% CI 16–43) in the high-risk group and 73% (64–83) in the low-risk group. The predictor performances were confirmed in each of the individual validation cohorts (aHR comparing high-risk to low-risk groups 2·57 [95% CI 1·65–4·01] in cohort 1; 2·12 [1·32–3·9] in cohort 2; and 2·11 [1·01–4·41] in cohort 3). In the combined validation cohort, the median progression-free survival was 3·1 years (95% CI 2·4–4·8) in the high-risk group and 10·8 years (10·1–not reached) in the low-risk group (p=0·0001). The risk of lymphoma progression at 2 years was 38% (95% CI 29–46) in the high-risk group and 19% (15–24) in the low-risk group. In a multivariate analysis, the score predicted progression-free survival independently of anti-CD20 maintenance treatment and of the FLIPI score (aHR for the combined cohort 2·30, 95% CI 1·72–3·07).

Interpretation We developed and validated a robust 23-gene expression-based predictor of progression-free survival that is applicable to routinely available formalin-fixed, paraffin-embedded tumour biopsies from patients with follicular lymphoma at time of diagnosis. Applying this score could allow individualised therapy for patients according to their risk category.

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Introduction

Follicular lymphoma is the most common indolent lymphoma and is characterised by prolonged median survival, usually exceeding 10 years.1 Treatment options range from watchful waiting to CD20-directed immunotherapy, alone or in combination with chemotherapy.2 New non-cytotoxic combinations are also being evaluated.3 Patient outcomes are, however, highly heterogeneous, and a substantial proportion of patients are at risk of early progression or transformation into high-grade lymphoma.4 Follicular lymphoma are at risk of early progression or transformation, and a substantial proportion of patients being evaluated.3 Patient outcomes are, however, highly heterogeneous, and a substantial proportion of patients are at risk of early progression or transformation into high-grade lymphoma.4 Follicular lymphoma is characterised by prolonged median survival, usually exceeding 10 years.1 Treatment options range from watchful waiting to CD20-directed immunotherapy, alone or in combination with chemotherapy.2 New non-cytotoxic combinations are also being evaluated.3 Patient outcomes are, however, highly heterogeneous, and a substantial proportion of patients are at risk of early progression or transformation into high-grade lymphoma.4 Follicular lymphoma are at risk of early progression or transformation, whereas others focused on somatic alterations in single genes, affecting the global transcriptional profile and outcome. The seminal study by the Leukemia/Lymphoma Molecular Profiling Project highlighted the role of non-malignant tumour-infiltrating cells on follicular lymphoma prognosis in the pre-rituximab era, enabling the building of a molecular predictor of overall survival on the basis of two expression signatures of immune response (IR1 and IR2). In another study, a T-cell signature of favourable prognosis was identified and a proliferation signature was associated with relapse. Other groups, using RT-PCR or immunohistochemistry, have remained controversial, sometimes with conflicting results and in heterogeneously subsets on the risk of disease progression or death but sometimes with conflicting results and in heterogeneously treated patient cohorts. Several other studies focused on molecular alterations driving histological transformation. One study group identified the role of an embryonic stem-cell signature probably sustained by MYC activation in transformed follicular lymphoma. Another group pinpointed six signatures related to the NF-κB pathway, with high scores found in biopsies preceding transformation, although not necessarily detected at the time of diagnosis. Finally, other investigators identified the clinical significance of somatic alterations or expression pattern, or both, in single genes.

Although not directly linked to our gene expression-focused research in context

Evidence before this study

We searched PubMed on Aug 15, 2017, with no date restrictions, for all original research (ie, excluding reviews) with the terms “follicular lymphoma” in the title, “gene expression OR expression signature” in the title or abstract, and “prognosis OR prognostic OR prediction OR predictive OR progression OR risk OR transformation OR survival” anywhere in the text. This search identified 52 articles. The relevant articles addressing the effect of gene expression on outcome in patients with follicular lymphoma were of two types: some studies used transcriptome-wide profiling to identify signatures predictive of progression, death, or histological transformation, whereas others focused on somatic alterations in single genes, affecting the global transcriptional profile and outcome. The seminal study by the Leukemia/Lymphoma Molecular Profiling Project highlighted the role of non-malignant tumour-infiltrating cells on follicular lymphoma prognosis in the pre-rituximab era, enabling the building of a molecular predictor of overall survival on the basis of two expression signatures of immune response (IR1 and IR2). In another study, a T-cell signature of favourable prognosis was identified and a proliferation signature was associated with relapse. Other groups, using RT-PCR or immunohistochemistry, have remained controversial, sometimes with conflicting results and in heterogeneously subsets on the risk of disease progression or death but sometimes with conflicting results and in heterogeneously treated patient cohorts. Several other studies focused on molecular alterations driving histological transformation. One study group identified the role of an embryonic stem-cell signature probably sustained by MYC activation in transformed follicular lymphoma. Another group pinpointed six signatures related to the NF-κB pathway, with high scores found in biopsies preceding transformation, although not necessarily detected at the time of diagnosis. Finally, other investigators identified the clinical significance of somatic alterations or expression pattern, or both, in single genes.

Although not directly linked to our gene expression-focused search, new clinico-genetic predictors combining the mutational status of several genes with the Follicular Lymphoma International Prognostic Index (FLIPI) score (m7FLIPI and POD24-PI) have been proposed to improve the identification of patients at high risk of progression.

Added value of this study

To overcome the limitations of previous studies due to heterogeneous treatment cohorts, small size, or no validation cohorts, we did a progression-free survival-supervised analysis of expression data obtained in a large cohort of patients in the setting of a clinical trial. We identified a 23-gene score able to predict the risk of progression in patients with follicular lymphoma at diagnosis, independently of the FLIPI score and use of anti-CD20 maintenance therapy. Importantly, we developed this predictor to be fully applicable to routinely available formalin-fixed, paraffin-embedded biopsies. Moreover, results were further validated in three independent international cohorts of patients homogeneously treated with immunochemotherapy. To the best of our knowledge, this is the largest study to date of gene-expression profiling to predict the risk of progression of patients with follicular lymphoma receiving first-line immunochemotherapy, confirmed in three independent cohorts. Furthermore, we identified a gene signature characteristic of B-cell centroblasts that was prognostic, underlining that in addition to the tumour microenvironment, tumour B-cell biology contributed to the clinical aggressiveness of the disease.

Implications of all the available evidence

Despite recent progress in the stratification and management of patients with follicular lymphoma, a substantial proportion of patients are still underserved by existing standard treatment and have rapid progression of their disease. Our gene-expression predictor could be valuable in the clinical setting to identify patients at high risk or low risk of progression so as to adjust the therapeutic strategy and enrolment for innovative treatments.
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