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Diffuse Large B Cell Lymphoma: From Gene Expression Profiling to Prediction of Outcome

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ABSTRACT

Diffuse large B cell lymphoma (DLBCL) is a subtype of non-Hodgkin lymphoma (NHL), characterized by a markedly heterogeneous clinical course and response to therapy that is not appreciated with standard histopathologic and immunophenotypic evaluations. Recent studies have focused on the use of genome-scale expression profiles that provide a snap fingerprint of the tumor and identifying tumors with similar genetic alterations and clinical features. Gene expression studies have the ability to recognize distinct subgroups of patients based on similar molecular characteristics and markedly different outcomes that were independent of the International Prognostic Index (IPI). Further, DNA microarray studies also allow identification of new prognostic biomarkers in DLBCL. However, new methods for immunohistochemical analysis of tissue microarray and RNA extraction from paraffin-embedded blocks are required to overcome the major pitfall of this technology—the requirement for fresh tissue. Herein, we summarize the progress made in better prediction of prognosis of DLBCL patients as a result of gene expression profiling.
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KEY WORDS

Prognostic biomarkers • DLBCL • gene arrays

INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) is the most common adult non-Hodgkin lymphoma (NHL), with an annual incidence of >25,000 cases in the United States [1]. Although DLBCL has characteristic morphology, marked immunophenotypic, cytogenetic, and molecular heterogeneity underlies the variable clinical outcome of DLBCL patients. Clinical surrogates, such as the International Prognostic Index (IPI) [2], although highly useful, do not adequately capture the molecular and cellular variability that affects clinical behavior of DLBCL. Biologic mechanisms underlying DLBCL pathogenesis are complex, and involve intricate relationships between multiple genes, signaling pathways, and regulatory processes [3]. Elucidation of DLBCL pathogenesis is necessary to allow recognition of new molecular therapeutic targets, discovery of DLBCL subgroups with distinct clinical outcomes, and identification of molecular prognostic markers that may more accurately predict DLBCL outcomes. Accomplishment of these goals is of paramount importance, and may form the basis for future risk-adapted treatments. Historically, attempts to elucidate DLBCL pathogenesis or identify new prognostic markers utilized a single gene approach. However, the latter cannot account for the complex multigene processes underlying DLBCL pathogenesis, and thus do not accurately reflect the complex changes observed in these tumors. Consequently, new investigational tools enabling simultaneous evaluation of multiple components of these biologic processes might further advance our understanding of DLBCL and potentially lead to specific molecularly targeted and patient-tailored therapies.

DNA microarrays are a new technology used to measure the expression of tens of thousands of genes simultaneously, enabling a more comprehensive evaluation of gene expression. This technique allows the comprehensive analysis of messenger RNA (mRNA) expression in tumor samples. The clinical characteristics and behavior of a tumor are determined by the specific genetic changes present in the tumor

cells that are reflected in their pattern of mRNA expression creating a "molecular signature" or "fingerprint" for the tumor. The full potential of microarrays has not yet been realized; however, they may (1) identify previously unrecognized disease entities with distinct biologic and clinical features, (2) elucidate the key genetic profiles and lesions that define each of these new nosologic entities, (3) discover new molecular targets for future therapeutic intervention, (4) identify genes that play a potential role in determining prognosis, (5) discover previously unknown genes of major clinical relevance from numerous EST clones present on the arrays, and (6) identify gene expression signatures correlated with response to specific therapeutic agents. Herein, we briefly review the contribution of gene expression profiling and its role in prediction of outcome of DLBCL patients.

Less than half of the patients with DLBCL will be cured with conventional chemotherapy regimens [4,5]. Improvement in disease-free and overall survival (DFS, OS) may be obtained with the addition of monoclonal antibodies (mAb), such as rituximab [5]. Although standard pathologic techniques do not reliably predict sensitivity to chemotherapy or outcome for individual patients, gene expression profiling has provided important insights into the biology of DLBCL, allowing a better molecular classification of tumors that are more homogeneous in pathogenesis and clinical behavior.

The pivotal microarray study was performed by Alizadeh et al. [6] with the use of a cDNA Lymphochip array. The evaluation of tumors from 42 DLBCL patients treated with anthracycline-based chemotherapy led to the identification of 2 distinct subgroups based on the expression of genes characteristic of germinal center B cells (GC) or in vitro-activated peripheral blood B cells (ABC). Patients with GC subtype had a significantly better 5-year OS (76% versus 16%, $P < .01$), independent of the IPI score. These findings were further confirmed by the larger Lymphoma and Leukemia Molecular Profile Project (LLMPP) study [7]. Using a similar cDNA Lymphochip array platform, analysis of tumor samples from 240 DLBCL patients treated with anthracycline-based chemotherapy demonstrated a significant difference in the 5-year OS between the GC-like and ABC-like subgroups (60% versus 35%, respectively). Although the early microarray expression profile studies were able to identify the presence of biologically distinct subgroups of DLBCL, they were unable to identify the relative contribution of individual genes, therefore making it difficult to build clinically useful prognostic models based on a relatively small number of genes. To address this question, both the Rosenwald [7] and Shipp groups [8] applied supervised analytic methodologies to the Lymphochip and Affymetrix-derived gene expression profiles of 240 and 58 DLBCL patients, respectively. This approach led to construction of outcome predictors based on expression of 17 and 13 genes, respectively. However, there was no overlap between the lists of genes comprising these 2 outcome prediction models. This disparity between large genome-scale expression profile models has been attributed to patient selection, technical differences, arrays composition, and variable analytical approaches. Wright et al. [9] designed a method based on Bayes' rule that could be used to translate experimental results across different microarray platforms. Expression data from 14 genes identified by the LLMPP [7] and analyzed by Shipp et al. [8] were able to subdivide patients into GC-like and ABC-like, with significant different outcomes. Nevertheless, despite the positive results, this model may not be clinically useful because of complex manipulations with shifting and scaling of gene expression from Affymetrix data to match the mean and variance of the corresponding expression values in the cDNA microarray dataset.

In an attempt to devise a technically simple method that could be applicable for routine clinical use, we evaluated the mRNA expression of 36 genes previously reported to predict survival [10] in tumor specimens from 66 DLCBL patients treated with anthracycline-based therapy. The top 6 genes ranked according to their predictive power on univariate analysis were used to construct a model based on their relative individual contribution into a multivariate analysis. Among the selected genes, *LMO2*, *BCL-6*, and *FN1* predicted longer survival, whereas *CCND2*, *SCYA3*, and *BCL-2* predicted shorter survival. Based on the expression of these 6 genes, patients could be subdivided into IPI-independent low-, intermediate-, and high-risk groups with significantly different 5-year OS rates ranging from 65% in the low-risk to 15% in the high-risk subgroups. This model was subsequently validated in the data sets available from previously reported studies [7,8].

However, gene expression arrays are not widely available, require fresh tumor specimens, and are labor-intensive and expensive. Therefore, researchers have tried to use the information derived from RNA profiling studies to create prediction models based on more amenable techniques such as immunohistochemistry (IHC). However, multiple IHC studies have led to contradictory results [11,12], suggesting the lack of an ideal set of IHC markers for outcome prediction in DLBCL. Hans et al. [13] complimented cDNA microarrays with immunohistochemistry (IHC) staining. They proposed an IHC model based on 3 markers: CD10, *BCL-6*, and MUM1 for determination of GC-like and ABC-like DLBCL subtypes. This model demonstrated positive predictive values of 87% and 73% for correctly identifying GC-like and ABC-like DLBCL subtypes and could predict patient survival: 76% of IHC-defined GC-like DLBCL

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