Molecular Diagnostics of Lymphoma: Coming of Age

Aru W Sudoyo

Molecular diagnostics, defined as the use of diagnostic testing to understand the molecular mechanisms of an individual patient’s disease, has seen phenomenal progress in the last 15 years. Already accepted as essential to the delivery of safe and effective therapy for many diseases in the future, it has crossed from the research laboratory to the clinic, and many diseases – and not just malignancies or cancer – will benefit from its use.

Malignant Non-Hodgkin’s lymphomas are no exception. Clonal, uncontrollably expanding, and with destructive proliferations of lymphoid cells, its complexity is reflected in its various (changes in the) classifications – from Ann Arbor to the REAL classification – spanning several decades. The aforementioned classifications showed how heterogeneous and difficult it is in not only in the diagnosis of the disease(s) but in its treatment. It has revealed itself as a multicomponent and multicompartmental disease, as hard to diagnose as to treat. Multidrug resistance (MDR) is one of the consequences of its heterogeneity, and the elucidation of its characteristics and behaviour is of paramount importance.

Advances in molecular biology techniques in recent years have given researchers the necessary tools previously inaccessible, thus providing them with the capability to open new horizons and answer questions which years ago were regarded as mysteries.

The techniques for molecular analysis have been borrowed from the benches of “basic science” research, and proven to be powerful tools for clinicians, i.e.:

I. Tests for Genome-Wide Screening of Chromosomal Abnormalities
   • Spectral karyotyping (multicolor fluorescence in situ hybridization)
   • Comparative genomic hybridization

II. Tests Targeting Specific Chromosomal Abnormalities
   • PCR (polymerase chain reaction analysis of DNA)
   • RT-PCR (reverse transcriptase PCR analysis of RNA)
   • Real-time PCR (automated PCR)
   • Genotyping for single nucleotide polymorphisms (PCR-SSP)
   • Fluorescence in situ hybridization (FISH)

III. Tests for Gene Expression Profiling
   • Global microarrays
   • Focused microarrays
   • Microarray of amplified RNA from microdissection

IV. Molecular Tests for Minimal Residual Disease Detection
   • Nested PCR
   • Quantitative real-time PCR (Q-PCR or Q-RT-PCR)

An example can be found in the evolution of indolent lymphomas to aggressive histologies, a situation known as histologic transformation (HT), and is frequently encountered in all subtypes of low grade B cell lymphoproliferative disorders. In the literature, HT develops in approximately 3% per year in patients with indolent lymphomas. Having a clinically rapid change in behaviour, HT causes a low grade disease turn into a highly proliferative malignancy with a poor prognosis. A result of multiple cytogenetic abnormalities, to date there are no biologic or genetic parameters of its development. Many genetic lesions have been identified in HT, and provide insight into its pathogenesis. These include genes regulating proliferation (C-MYC and CMYC-regulated genes); control of the cell cycle (CDKN2a and CDKN2B); and programmed cell death (TP53, C-MYC, and BCL2). Expression of the Bcl-2 protein has been described in the literature as an important prognostic factor which is independent of the clinical parameters of the International Prognostic Index (IPI), and rearrangement of the bcl-6 gene almost equally important in its own right.
Two original investigations in this issue of the Indonesian Journal of Internal Medicine have caught the attention of the editors and are highlighted in this editorial.

The first article, a study on gene rearrangements in follicular lymphoma among Indonesians by Oehadian, based the investigation on the premise that rearrangements of Bcl-2, bcl-6 and paired homeobox have important roles in the management of lymphoma. Their finding that Bcl-2 rearrangements are found to be commonly found in Indonesian lymphoma patients—higher in incidence than in other Asian regions—highlights the importance of molecular epidemiology in describing a population’s characteristics. The study was also special in that it was a collaboration with Japanese researchers.

The second article by Purwanto and his co-researchers, himself also a clinician as Oehadian, reported on the determination of EBNA-1 (from the EBV virus) in the tissues of patients with diffuse large B-cell lymphoma. His findings that 50% of study subjects were positive for EBNA-1 and correlated with bcl-2 expression, revealed a potentially characteristic feature of our (Indonesian) lymphoma population.

The reason for choosing the two abovementioned articles for the topic of this editorial was—to this editor’s opinion—a timely one, as we are now in the era in which two different areas, the laboratory bench and clinical ward, are now intertwined, more and more inseparable in the advancement of knowledge. But the bottomline of this discourse is that we are all proud of these Indonesian colleagues who— with all the limitations and constraints put upon them as “Third World physicians”—dared to jump in and be at the forefront of basic research with the rest of the world.

REFERENCES