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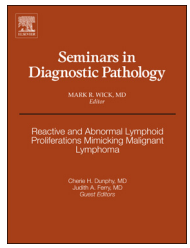

Hematological diseases: Prototypical conditions requiring the diagnostic and prognostic use of molecular data

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ABSTRACT

The field of diagnostic hematopathology is dynamic and evolving given the ongoing accumulation of molecular information and demand for integration of this information into routine clinical practice. In light of this molecular revolution, the appropriate and effective utilization of molecular studies by clinicians/pathologists is of paramount importance to the current diagnosis, prognosis, and monitoring of nearly all hematologic diseases. In the routine workup of certain hematologic neoplasms, it is more pertinent and practical to understand the purpose of these analyses and how to generally apply them to particular diseases rather than trying to remember a likely outdated list of genes. We will see advances in the treatment of hematologic malignancies as drug development catches up to our molecular understanding of diseases.

Introduction

The field of diagnostic hematopathology is dynamic and evolving given the increasing accumulation of molecular information and demand for integration of this information into routine clinical practice. In light of this molecular evolution, the appropriate and effective utilization of molecular studies by clinicians/pathologists is of paramount importance to the current diagnosis, prognosis, and monitoring of nearly all hematologic diseases.[1] In the routine workup of certain hematologic neoplasms, knowledge and proper application of evidence-based molecular tests by pathologists is considered standard of care. However, given the bewildering number of cytogenetic-, fluorescence in situ hybridization (FISH)-, and PCR-based molecular discoveries, maintaining ones competency can be challenging.

As there are space limitations, we are unable in this review to discuss the use of molecular data in all pertinent hematologic disorders for diagnosis, prognosis, and/or therapeutics. Therefore, as of late 2011, we present a summary table addressing generally accepted molecular testing in selected representative hematologic disorders (Table 1) and then focus on four prototypic hematologic disease entities for further discussion: chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and plasma cell myeloma (PCM).[2] These hematopoietic entities to be discussed were selected due to a relatively frequent occurrence in routine clinical practice and well-established role of molecular testing. A review of the morphologic diagnostic criteria is beyond the scope of this article.

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Table 1 – Molecular testing in hematologic neoplasms: disease examples with diagnostic, prognostic, and therapeutic significance (not all inclusive).[a]

Disease	Cytogenetics	Genes involved	Methods to detect	Comments
Diagnostic significance				
CML	t(9;22)(q34;q11.2)	*BCR–ABL1*	Cytogenetics, FISH, and RT-PCR	MRD; not specific for CML (subset of B-LL and rare de novo AML)
MPN		*JAK2* V617F	PCR	Not specific for MPN
MCD		*KIT* D816V	PCR	Can also be seen in solid tumors
CEL		4q12 (cryptic)	*FIP1L1–PDGFRA*	FISH
APL	t(15;17)(q24;q12)	*PML–RARA*	Cytogenetics, FISH, and RT-PCR	MRD
AML	Multiple abnormalities (see Table 4)		Cytogenetics, FISH, and PCR	MRD
MCL	t(11;14)(q13;q32)	*IGH–CCND1*	FISH and RT-PCR	Can also be seen in myeloma
HGBCL	t(8;14)(q24;q32)	*IGH–MYC*	FISH	Can also be seen in myeloma
		BCL2 rearrangement	FISH	
		BCL6 rearrangement	FISH	
T-PLL	inv(14)(q11q32)	*TCL1*	Cytogenetics and FISH	
ALCL	t(v;2p25)	*ALK*	FISH	Not specific for ALCL; can be seen in DLBCL, solid tumors, and IPT
Disease	Cytogenetics	Genes/genetic loci involved	Methods to detect	Prognosis
Prognostic significance				
CLL (see Table 2 for more details)	Del(17p13)	*TP53*	FISH	Unfavorable
	Del(11q22.3)	*ATM*	FISH	Unfavorable
	Trisomy 12		Cytogenetics and FISH	Intermediate
	Isolated del(13q)		FISH	Favorable
		IGHV mutational status	PCR	Unfavorable if unmutated; favorable if mutated
AML (see Table 4 for more details)	t(8;21)(q22;q22)	*RUNX1–RUNX1T1*	Cytogenetics and FISH	Favorable
	inv(16)(p13.1q22)	*CBFB–MYH11*	Cytogenetics and FISH	Favorable
	Complex karyotype		Cytogenetics	Unfavorable
PCM (see Table 5 for more details)	Hyperdiploid (trisomies of odd-numbered chromosomes)		Cytogenetics	Standard risk
	Hypodiploid		Cytogenetics	Unfavorable
	t(11;14)(q13;q32)	*IGH–CCND1*	FISH	Standard risk
	t(4;14)	*FGFR3*, *MMSET*, and *IGH*	FISH	Less favorable
	t(14;16)	*IGH–MAF*	Cytogenetics	Unfavorable
		Monosomy 13		
	Del(17p13)	*TP53*	FISH	Unfavorable
MDS (see Table 6 for more details)	Isolated del(5q)		Cytogenetics	Favorable
	Isolated del(20q)		Cytogenetics	Favorable
	Normal		Cytogenetics	Favorable
	Complex (>3 abnormalities)		Cytogenetics	Unfavorable
	Chromosome 7 abnormalities		Cytogenetics	Unfavorable