Personalized lymphoma diagnosis and treatment: recent advances

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Abstract

Comprehensive gene expression and genetic analysis of lymphoma during the last decade has revealed activated signaling pathways that can be targeted with specific drugs. In addition, novel antibodies have been developed to specifically target lymphoma cells. This article reviews these recent developments and discusses the potential consequences for diagnosis of lymphoma.

Keywords lymphoma; mutation

Introduction

Modern lymphoma diagnosis started with an international consensus that recognized that lymphoma consisted of a multitude of distinct diseases that only could be diagnosed correctly by integrating histology, immunophenotypic and genetic analysis with clinical data.[1] This paradigm was embraced by the W.H.O. and resulted in the internationally accepted W.H.O. classification of tumors of the hematopoietic and lymphoid tissues of which the last update was published in 2008.[2] At the same time, the human genome project had been initiated in 1990 and has long since been completed. The latter, together with great advances in high throughput DNA technology and analysis software, has made the genetic analysis of tumors possible on a genomic scale. Tumor genome-wide gene expression analysis, exome sequencing or total genome sequencing at great depth of sequencing, genome-wide epigenomic studies as well as chromatin immunoprecipitation studies combined with massive parallel sequencing have allowed to map the genomic alterations in tumors, including lymphoma. This has resulted in an avalanche of new knowledge during the last decade, as evidenced by the high number of publications on lymphoma in high profile journals. Alizadeh et al. were the first to analyze lymphomas by genome-wide gene expression analysis.[3] Of interest, their results confirmed the validity of the lymphoma classification paradigm by showing that lymphoma gene expression patterns segregated along recognized lymphoma types. However, their data as well as subsequent gene expression and genome sequencing data also showed more clearly than before that distinct lymphoma types as defined by the W.H.O were as yet heterogeneous and that this heterogeneity was reflected in a markedly different survival for groups of patients diagnosed with the same lymphoma type. This will be further commented on in this review. In addition, one of the major discoveries has been that distinct lymphoma types show, for the most, multiple gene alterations that converge upon constitutional activation of defined molecular pathways that are normally active in non-neoplastic lymphocyte subsets (Table 1). In addition, it has also been recognized that some lymphoma types show a high frequency of mutations affecting chromatin modification (Table 2). Some of the mutations were already discovered before the recent revolution in DNA technology, but most were not. For the first time complete maps of the spectrum of mutations can now be made for the distinct lymphoma types. Also, these discoveries have led to the development of novel drugs targeted at the molecular cell pathology (Table 3). Clinical studies with these drugs are currently being performed. These drugs are mainly kinase inhibitors or more generally pathway inhibitors, proteasome inhibitors and histone-deacetylase (HDAC) inhibitors, histone methyl transferase inhibitors and inducers of apoptosis.[4,5] Irrespective of the results obtained by the detailed molecular dissection of lymphoma and the windows it opens for novel therapy, therapy has also progressed that is not based on genetic research. The success of anti-CD20 antibody therapy for a broad range of B-cell lymphoma has spurred the development of alternative antibodies against other B cell surface molecules as well as T cell surface molecules and even bi-specific antibodies targeting B as well as T cells (Table 4). Some of these antibodies are radiolabelled or conjugated to drugs. Of interest, also bacteria, so-called Trojan-horse bacteria have been engineered to express antibodies to specifically target lymphoma cells and deliver cytotoxic substances. For many of these novel drugs, trials are being conducted and therefore their use has as yet not been clearly defined.

In this review, some of the lymphomas will be discussed of which we have gained the most new knowledge that may result in novel more targeted treatment. It is very likely that the latter will also need more detailed and 'personalized' lymphoma diagnostics.

Diffuse large B cell lymphoma

Diffuse large B cell lymphoma is the most common non-leukemic lymphoma type with an incidence of 3–4/100000 person-years. It is a clinically aggressive lymphoma and had long been suspected to consist of subtypes with distinct biologies. Largely thanks to genome-wide gene expression analysis as well as genetic analysis at least three distinct entities have been recognized: primary mediastinal large B cell lymphoma (PMBL) (Figure 1), diffuse large B cell lymphoma (DLBCL), not otherwise specified (NOS) (Figure 2), with an origin from germinal center cell B cells (GCB) and DBLCL with an origin from activated B cells (ABC).[3,6]

PMBL is a disease of younger, mostly female patients, occurring most frequently in the third decade of life. The disease affects the anterior mediastinum similar to nodular sclerosis Hodgkin lymphoma with which it also shows a similar gene expression pattern, genetic aberrancies in chromosome region 9p24 and the mutation of the PTPN1 gene, the significance of which is as yet not clear.[7,8] The 9p24 chromosomal region shows amplification of PD-1 ligands 1 and 2 as well as of JAK2. Amplification of JAK2 increases its expression and activates the

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The most frequent mutations in B cell lymphoma affecting major B lymphocyte signaling pathways

Pathway	Gene	DLBCL	BL	LPL	SMZL	MCL	CLL	HCL
B-cell receptor signaling pathway	CD79A (m)	20%	—	—	1%	—	—	—
	CD79B (m)	20%	—	—	—	—	—	—
	CARD11 (m)	10%	—	—	—	—	—	—
	TCF3 (m)	3%	70%	—	—	—	—	—
	ID3 (m)	—	70%	—	34%	—	—	—
Toll-like receptor signaling pathway	MYD88 (m)	30%	5%	90%	10%	—	3%	—
Notch signaling pathway	NOTCH1 (m)	8%	—		5%	12%	11%	—
	NOTCH2 (m)	8%	—	—	20%	5%	—	—
	SPEN (m)	—	—	—	5%	—	—	—
	DTX1 (m)	—	—	—	2%	—	—	—
	MAML1 (m)	—	—	—	2%	—	—	—
	FBXW7 (m)	—	3%	—	—	—	2%	—
NF-κB signaling pathway	TNFAIP3 (m/d)	30%	—	40%	7%	44%	—	—
	IKBKB (m)	—	—	—	7%	—	—	—
	BIRC3 (m/d)	—	—	—	10%	6%	4%	—
	TRAF3 (m/d)	—	—	—	5%	—	—	—
MEK/ERK signaling pathway	BRAF (m)	4%	—	—	—	—	—	100%
	ATM (m/d)	—	—	—	—	41%	—	—
	CCND1 (m)	—	—	—	—	35%	—	—

DLBCL: diffuse large B cell lymphoma; BL: Burkitt lymphoma; LPL: lymphoplasmacytic lymphoma; SMZL: splenic marginal zone lymphoma; MCL: mantle cell lymphoma; CLL: chronic lymphocytic leukemia; HCL: hairy cell leukemia; m: mutation; d:deletion.

Table 1

JAK2/STAT signaling pathway leading to cell growth. JAK2 inhibitors, novel drugs mainly used for myeloproliferative disease, are drugs that likely also will be effective for the treatment of primary mediastinal large B cell lymphoma as proven also by preclinical studies.[9] The correct diagnosis of PMBL is therefore of importance. This diagnosis can reliably be made using immunohistochemistry and taking into account the typical clinical presentation. However, the diagnosis may be more difficult or even impossible to establish when dealing with a biopsy taken from a non-mediastinal mass such as e.g. a supraclavicular lymph node. Novel immunohistochemical markers such as MAL or more recently and perhaps more promising PD-1 ligand 2 (PDL-2) seem to be a reliable immunohistochemical markers for this disease.[10,11]

DLBCL, NOS is mainly a disease of the elderly with a peak incidence in the seventh decade for the subtype derived from germinal center cell B cells and the eighth decade for the subtype derived from activated B cells. Gene expression analysis has shown that the ABC subtype expressed genes typical of activated B cells such as IRF4. Similarly, the GCB subtype expressed genes associated with germinal center cell B cells such as LMO2, CD10 and BCL6.[3] These two subgroups of DLBCL show a different survival when treated with CHOP or R—CHOP, the germinal center cell derived subgroup showing better survival than the activated B cell subtype.[12,13] Of interest, distinct genetic changes have also emerged between the two subgroups, corroborating the validity of dividing diffuse large B cell lymphoma according to cell of origin. CD79a, CD79b, CARD11, MYD88 and TNFAIP3 mutations are predominantly seen in diffuse large B cell lymphoma of activated B cell type. These mutations have in common that all activate the NF-κB pathway resulting in lymphoma growth.[14,15] By contrast, diffuse large B cell lymphoma of

The most frequent mutations in B cell lymphoma affecting chromatin modification

Gene function	Gene	DLBCL	FL	MCL
Histone methyl transferases	MLL2 (m)	32%	89%	14%
	EZH2 (m)	5.6%	27%	—
	WHSC1 (m)	—	—	10%
Histone acetylases	MEF2B (m)	11.4%	13.4%	—
	CREBBP (m)	18%	32.6%	—
	EP300 (m)	10%	8.7%	—

DLBCL: diffuse large B cell lymphoma; FL: follicular lymphoma; MCL: mantle cell lymphoma; m: mutation.

Table 2