REVIEW ARTICLE

Diffuse Large-Cell Lymphoma Part I: Clinical Features, Histology and Prognosis

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Lymphomas are malignant transformations of normal lymphoid cells that reside predominantly in lymphoid tissues such as lymph nodes as well as extranodal sites such as stomach, thyroid, and bone. The malignant lymphomas represent a heterogeneous group of disorders which vary in their clinical presentation and in their potential for cure (1). They are morphologically subdivided into two major categories: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma. The NHLs in turn are broadly divided into aggressive and indolent (also known as low grade) histologies. The aggressive NHL represent about 50% of the NHLs diagnosed in Western countries, and the most common subtype is diffuse large B-cell lymphoma. The aggressive lymphomas can arise from either B, T or NK lymphocytes. We will discuss the prognosis and management of de novo diffuse large B-cell lymphoma (DLCL-B), which should be set apart from transformed DLCL-B and from divergent histologies.

De novo diffuse large-cell lymphoma (DLCL)

Those cases who, without a prior history of lymphoma, are diagnosed for the first time with DLCL are considered as having de novo DLCL. De novo DLCL should be set apart from transformed DLCL (to be discussed below) which occurs after an indolent NHL transforms to DLCL. The prognosis of the latter disorder is less favorable than for de novo DLCL. One of the important features of de novo DLCL is that after completing chemotherapy and achieving a complete remission (CR), for the most part they are considered cured if they are able to maintain that remission continuously for 24 months (2-4).

From this point on, we will refer to de novo diffuse large B cell lymphoma as DLCL-B. This is the most common histologic subtype of NHL accounting for approximately 25% of cases. In the United States, the incidence of DLCL-B is approximately 7 cases per 100,000 person years. Like most other NHLs, there is a male predominance. Incidence increases with age; the median age at presentation is 64 years. DLCL-B is a heterogeneous group of tumors consisting of large, transformed B-cell with prominent nucleoli and basophilic cytoplasm, a diffuse growth pattern and a high proliferation index. The tumor cells often resemble normal centroblasts or immunoblasts. The most frequent type of DLCL-B is the common type arising from either lymph nodes or extranodal sites but there are some less common histologic and clinical variants which include:

- Anaplastic large-cell lymphoma
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- Large B-cell lymphoma, lymphomatoid granulomatosis type
- T-cell rich/histiocyte-rich large B-cell lymphoma

Of the above, the two most common variants are anaplastic large-cell and primary mediastinal large-cell which we will discuss in more detail below.

The immunophenotype of DLCL-B can be determined by immunohistochemistry or by flow cytometry. Immunohistochemistry is preferable since it is feasible to visualize directly the morphology of the stained cells which is not possible with flow cytometry. However, for determination of surface immunoglobulin clonality, flow cytometry is necessary. Nevertheless, determination of clonality is not usually necessary to establish a diagnosis of large-cell lymphoma while it is frequently necessary for lymphoproliferative disorders in which the cells are not morphologically abnormal such as chronic lymphocytic leukemia. Tumor cells in cases of DLCL-B usually express pan B-cell antigens (CD19, CD20) as well as others such as CD45, surface membrane IgM, and occasionally heavy chain isotypes. The bcl-2 protein can be expressed in 25%-80% of DLCL-B as well as bcl-6 protein in 70% of cases. The proliferation index, determined by Ki-67 or MIB-1 staining, is usually high (> 40%). The majority of DLCL-B tumors have genetic abnormalities, but there is no specific cytogenetic change that is typical or diagnostic although deletions of 6q are among the most common.

Most cases of DLCL-B demonstrate rearrangement of the immunoglobulin gene heavy and light chains and somatic mutations of the variable regions. The bcl-6 is a

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No relevant conflicts of interest

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gene located on chromosome 3, is rearranged in 20 to 40% of cases and shows mutations in the 5' noncoding region in 70%. Over twenty different translocations involving bcl-6 have been identified. Both 5' noncoding mutations of the bcl-6 proto-oncogene and immunoglobulin variable region gene mutations are found in normal germinal center cells; their presence in DLCL-B is consistent with a germinal center or post-germinal center stage of differentiation. The post germinal center cells are those found in the lymph node in between germinal centers (Figure 1). The 5' noncoding mutations abolish negative auto-regulation of expression by bcl-6, which is a transcriptional repressor, whereas the translocations replace the bcl-6 promoter with strong, constitutively active promoters derived from many different genes. The net effect of both the mutations and translocations is the same: the inappropriate over-expression of bcl-6.

The t(14;18) is also present in approximately 30% of patients with DLCL-B. Such cases might represent histologic transformations of a prior follicular lymphoma and can also be associated with discordant or divergent histologies (see below).

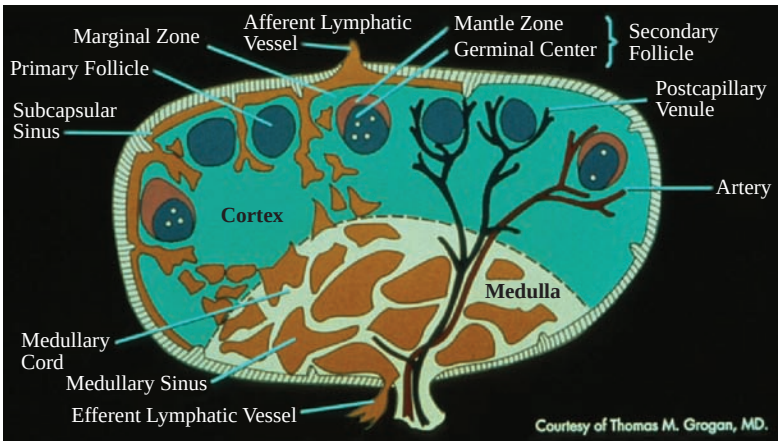

Figure 1. Microscopic structure of a normal lymph node

Anaplastic large-cell lymphoma

Anaplastic large-cell lymphoma (ALCL) is a T-cell or null cell NHL, although a B cell variant has been recognized by French pathologists (5). ALCL represents only about 2% of all NHLs in adults, but is the second most common T-cell lymphoma. This variant has been divided into two clinical subtypes, cutaneous and systemic. The median age of patients with primary systemic ALCL is 34, with a male predominance. There is a bimodal age distribution, with peaks in childhood/young adulthood, and again in late adulthood. In contrast, primary cutaneous ALCL accounts for approximately 10% of the cutaneous T-cell lymphomas, affects predominantly older adults and is rare in children. It is crucial to differentiate primary cutaneous ALCL from lymphomatoid papulosis (LP) which is a premalignant disorder that should not be treated with chemotherapy. This distinction is purely a clinical one since LP and cutaneous ALCL are identical histologically. The median age at diagnosis is 55 years. Two pathologic subtypes of systemic ALCL are recognized according to the presence of a translocation involving the Anaplastic Lymphoma Kinase gene known as ALK. Particularly in childhood and younger adults, a high fraction of ALCLs are associated with ALK translocations, while ALK negative systemic ALCLs are more common in older adults and their prognosis is not as favorable as for the ALK+ type. However, both are potentially highly curable neoplasms, contrary to what the term anaplastic would imply to most clinicians.

ALK is a receptor tyrosine kinase gene located on chromosome 2p23. The translocation, t(2;5) causes the fusion of the nucleophosmin (NPM) gene (5q35), coding for a nucleolar phosphoprotein, with the cytoplasmic domain of ALK on chromosome 2p23.

The tumor is composed of large blastic cells with round or pleomorphic, often horseshoe-shaped or "embryoid" nuclei with multiple or single prominent nucleoli. The cells have abundant cytoplasm, which gives them an epithelial or histiocyte-like appearance. Their anaplastic nature is a frequent source of confusion because ALCL can resemble non-lymphomatous disorders such as melanoma and malignant fibrous histiocytoma (MFH). Immunophenotyping has allowed pathologists to identify cases of ALCL which otherwise might have been erroneously diagnosed as melanoma or MFH. These tumors are CD30+ (also known as Ki-1). The "hallmark cell," which is classically identified with ALCL, has an eccentric nucleus and a prominent, eosinophilic golgi region, or paranuclear hof.

Primary mediastinal (thymic) large B-cell lymphoma

Primary mediastinal large B-cell lymphoma (PMLBCL) is a distinct clinicopathologic entity which arises from the thymic (medullary) B-cells. It has clinical features that are distinct from DLBCL. Primary mediastinal large B cell lymphoma comprises 7% of all diffuse large B-cell lymphomas (2.4 % of all NHLs). From the clinical standpoint, the most common characteristics, aside from the presence of an easily identified mediastinal

mass on chest x-ray (Figure 2), are the striking female predominance (2:1) and the young age at diagnosis, with virtually all patients falling into the range of 20-40 years old. The young age is probably due to the fact that the lymphocytic compartment of the thymus gland undergoes involution after 40 years of age. It is not clear why female gender predominates.

Patients present with a locally invasive anterior mediastinal mass originating in the thymus, with frequent airway compromise and superior vena cava (SVC) syndrome. A sign of SVC syndrome is the presence of collateral circulation over the chest wall which in advanced stages of SVCS can be very striking (Figure 3). A more subtle and early sign is the presence of small telangiectasiae over the chest wall, which unless the clinician is aware of and actively looks for, could go unnoticed. Those patients without clinically obvious SVC obstruction have evidence of compression of this vessel by computed tomography (CT) scan; in total, 80% have some evidence of SVC compromise.

Relapses tend to be very aggressive in behavior and frequently involved sites are extranodal, including the liver, gastrointestinal tract, kidneys, ovaries, and central nervous system. Although early studies suggested an unusually aggressive, incurable tumor, others have reported cure rates similar to those for typical DLBCL with aggressive therapy, usually combining chemotherapy with mediastinal irradiation.

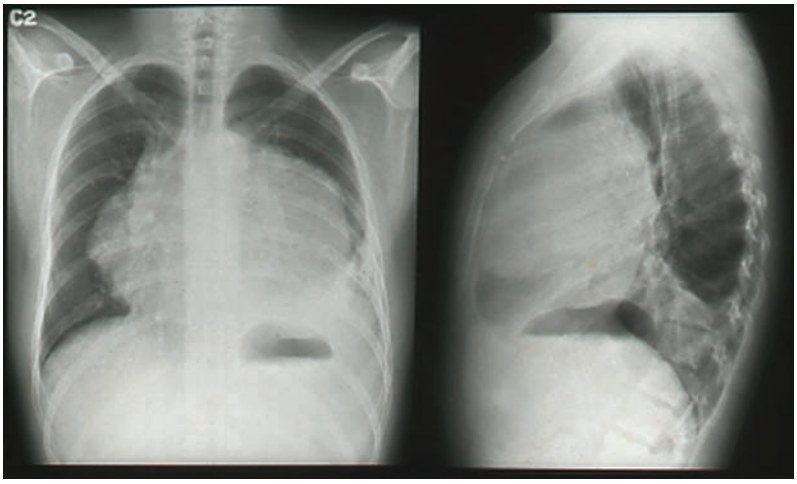

Figure 2. Chest films of a patient with primary mediastinal large-cell lymphoma. Note that in the lateral view the mass is seen in the anterior mediastinum, typical of this disorder that originates in the thymus gland.

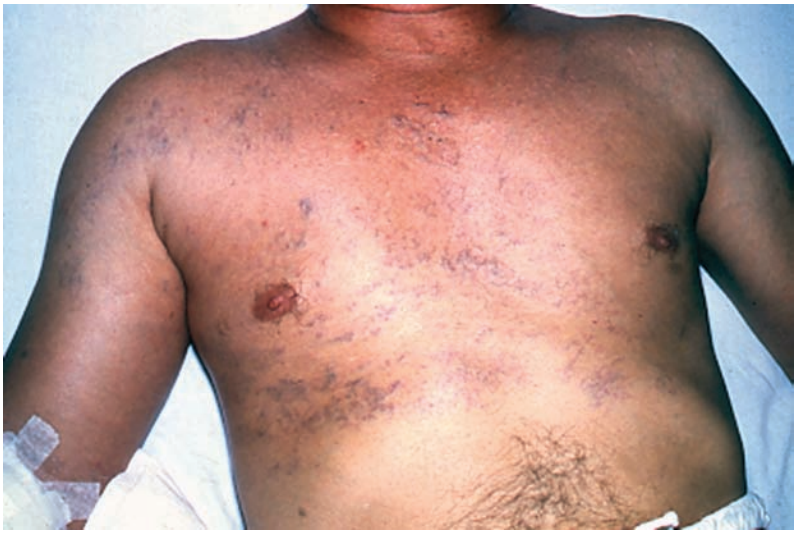

Figure 3. Patient with superior vena cava syndrome (SVCS). Note the telangiectases in anterior chest wall due to collateral circulation secondary to obstruction of venous flow. Telangiectasiae usually represents the first sign of SVCS and can be more subtle than in this figure.

Histologically, the tumor is composed of large-cells with variable nuclear features, resembling centroblasts, large centrocytes, or multilobated cells, often with pale or "clear" cytoplasm. Less often, the tumor cells resemble immunoblasts. Reed-Sternberg-like cells may be present. Many cases have fine, compartmentalizing sclerosis. However, it is impossible to make a diagnosis of PMLBCL without knowledge of the clinical picture because there is no pathognomonic histological feature. Consequently PMLBCL is a clinicopathological entity.

The tumor cells are usually Ig-, CD5-, and CD10-, but express B-cell-associated antigens (CD19, CD20, CD22, CD79a) and leukocyte common antigen CD45. The latter marker is important because sometimes there might be difficulty in differentiating PMLBCL from the grade II or syncitial variant of nodular sclerosing Hodgkin's disease which is usually CD45 negative. CD15 is usually not expressed in PMLBCL but is usually present in classical Hodgkin's disease. Expression of CD30 is often present, but is weak in PMLBCL but strongly expressed in classical Hodgkin's disease. The tumor cells also stain for TRAF-1 and nuclear c-rel. These two markers are also commonly expressed by the Reed-

Sternberg cells of classical Hodgkin lymphoma, but are uncommonly present in other forms of DLBCL.

Immunoglobulin heavy and light chain genes are rearranged. The bcl-2 gene is usually germline and bcl-6 gene rearrangements are uncommon. Amplification of the REL oncogene has been described in a minority of the cases. Hyperdiploid karyotypes, often with gains in the region containing the JAK2 gene on chromosome 9p, have been noted. Gene expression profiling has shown a similarity between the cell lines of primary mediastinal large B-cell lymphoma and classical Hodgkin lymphoma, a disorder with which it shares a number of clinical and laboratory features.

Transformed DLCL

Follicular lymphoma (FL) is a B-cell NHL with a relatively indolent clinical course. Frequently FL transforms histologically to DLCL-B after developing secondary genetic alterations at both nucleic acid and chromosomal levels. Histological transformation of FL to aggressive DLCL occurs in about 25% to 30% of patients after one or more relapses. This is most likely an underestimate since many patients at relapse are not biopsied. This transformation is usually associated with acceleration of the clinical course and shortened survival although this appears to depend on the prior treatment administered since patients who have not had prior exposure to doxorubicin appear to do better at the moment they transform (6). At histological transformation the malignant cells retain t(14:18), that is present in approximately 85-90% of these cells prior to transformation. In addition it has been shown that secondary chromosomal defects, such as mutations of the c-myc, p53, ras, bcl-2, bcl-6 genes, and allelic loss, mutation or hypermethylation of the p15 and the p16 genes may be associated with the transformed stage of FL (7). However, the genetic and/or epigenetic events that may initiate genome wide instability and acquisition of multiple genetic abnormalities of the tumor clone in histological transformation of FLs remain to be determined (7).

Divergent histologies

Divergent or discordant histologies is defined as the coexistence of a diffuse large-cell lymphoma in one site and a low-grade lymphoma in another site (2), such as bone marrow. Discordant histologies is a well recognized phenomenon. The coexistence of a low grade lymphoma with DLCL changes the prognosis because of the higher risk for a late relapse frequently instigated by the low grade component after eradication of the aggressive histology. In a large series of patients at MD Anderson Cancer Center with diffuse aggressive lymphoma, mostly diffuse large-cell-type, the late relapse rate of those who attained CR was 7%. There were several histologic features at presentation associated with higher risk of relapse: divergent histology, primary extranodal DLCL, and sclerosing large-cell lymphoma (LCL). Divergent histology was the most important feature that predisposed these patients to a late relapse.

Staging

The Ann Arbor staging system developed in 1971 for Hodgkin's lymphoma (HL) was adapted for staging NHLs. This staging system focuses on the location of lymph nodes involved and the presence or absence of systemic constitutional ("B") symptoms. The presence or absence of systemic symptoms should be noted with each stage designation. Constitutional symptoms are fever >38.3°C, drenching sweats, or weight loss >10% of body weight. Although Ann Arbor stage is an important prognostic feature in DLCL, it is not the only pertinent one and is not the most important one either, as will be discussed in detail below. However, prior to initiating therapy, every patient should be properly evaluated for extent of disease and the specific stage should be assigned. Staging evaluation should include a thorough physical examination, laboratory studies including complete blood count, chemistries including LDH, uric acid, β-2 microglobulin as well as bone marrow aspirate with flow cytometry for lymphoma markers and biopsy.

Role of PET scan

Positron emission tomographic (PET) scanning using 18-fluoro-2-deoxyglucose (FDG) appears to be highly sensitive and specific for detecting NHL in nodal and extranodal sites. PET scanning is useful in disease detection in most Hodgkin lymphoma variants especially the aggressive and highly aggressive NHL variants, while its overall usefulness in the indolent lymphomas remains unclear. However, in all indolent NHL variants, emergence of foci of intense uptake should raise suspicion of histologic transformation to a more aggressive NHL variant. Numerous studies have documented that PET scanning is capable of detecting metabolically active tumor cells in residual masses following or during chemotherapy, and that persistent abnormal uptake predicts for early relapse and/or reduced survival. PET or PET/CT scanning may be useful for initial staging and prognostic purposes, and may improve the accuracy of the International Workshop Criteria (IWC) as well as the prognostic value of the International Prognostic Index (IPI) (8) (Table 1). The use of an "early" PET scan (during treatment, rather than at its completion) has been shown to predict outcome after treatment. The PET scan can thus be considered as a post-treatment prognostic factor. A recent study performed

Table 1. New Response Criteria for NHL Using PET Scan Plus International Workshop Criteria

CR	CR by IWC with a completely negative PET
	CRu, PR, SD by IWC with a completely negative PET and a negative BMB if positive prior to therapy
	PD by IWC with a completely negative PET and CT abnormalities (new lesion, increasing size of previous lesion) > 1.5 cm (> 1.0 cm in the lungs) and negative BMB if positive prior to therapy
CRu	CRu by IWC with a completely negative PET but with an indeterminate BMB
PR	CR, CRu, or PR by IWC with a positive PET at the site of previously involved node/nodal mass
	CR, CRu, PR, or SD by IWC with a positive PET outside the site of previously involved node/nodal mass
	SD by IWC with a positive PET at the site of a previously involved node/nodal mass that regressed to < 1.5 cm if previously > 1.5 cm, or < 1 cm if previously 1.1-1.5 cm
SD	SD by IWC with a positive PET at the site of previously involved node/nodal mass (ie, residual mass)
PD	PD by IWC with a positive PET finding corresponding to the CT abnormality (new lesion, increasing size of previous lesion)
	PD by IWC with a negative PET and a CT abnormality (new lesion or 50% increase in size of previous lesion)

by investigators in Puerto Rico showed that the baseline PET SUV actually correlated better with clinical outcome in previously untreated patients with NHL as compared with the post-therapy PET scan. However, for previously treated patients treated with salvage chemotherapy, the post-therapy PET scan is still very predictive of long term outcome. In general, the FDG-PET/CT scan has become a standard tool in management of NHL (9).

Pre-treatment prognostic factors

Clinical oncologists should all be familiar with the prognostic factors relevant to each tumor type. Knowledge of these factors can be very useful in making treatment decisions. In addition, researchers designing clinical trials, especially randomized studies, have to use prognostic factors in order to obtain a balanced distribution of these predictive features in each treatment arm.

It is also essential to understand some basic principles regarding prognostic factors. These factors are clinically relevant when the prognosis of a given disorder is intermediate. It is easy to appreciate that if we achieve 100% cure rate, no prognostic factor will be relevant (Figure 4). A similar phenomenon will happen with a rapidly and uniformly lethal disorder in which no prognostic factor will be relevant. Another important principle is that prognostic factors will change as new treatments improve the outcome. As new treatments improve the prognosis of a given disorder some prognostic factors will disappear. For example with the introduction of Herceptin for treatment of Her-2+ breast cancer, the expression of Her-2, previously an important adverse prognostic feature, has lost much of its significance. Similarly with the introduction of Rituximab for management of DLCL-B, the significance of the International Prognostic Index (see below) has been altered.

International Prognostic Index

The Ann Arbor classification, used to determine the stage of this disease, does not accurately distinguish between patients with different long-term prognoses. The International Prognostic Index was developed to predict outcome in patients with aggressive NHL on the basis of the patients' clinical characteristics before treatment (10). The five pretreatment characteristics that remained independently significant in this model are: age (< 60 vs. > 60 years), tumor stage (stage I or II – localized disease vs stage III – advanced disease), the number of extranodal sites of disease (< 1 vs. > 1), performance status (0 or 1 vs. > 2), and serum LDH level (< 1 times normal vs. > 1 times normal). The international index and the age-adjusted international index should be used in the design of future therapeutic trials in patients with aggressive NHL and in the selection of appropriate therapeutic approaches for individuals patients (10). For example, patients with localized stage I presentation with a favorable IPI can be

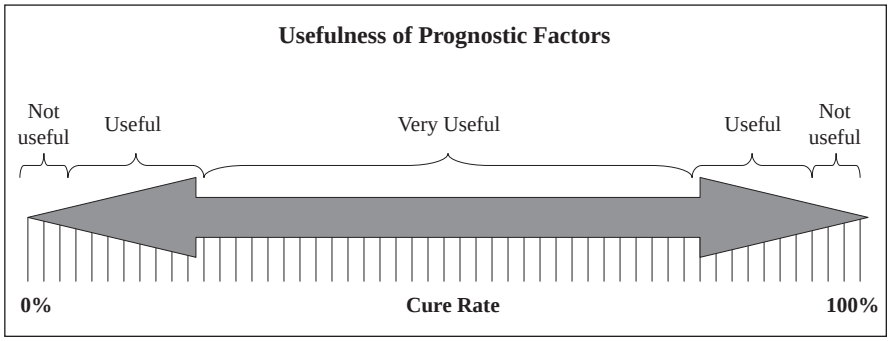

Figure 4. Prognostic factors are clinically relevant only when the prognosis of a given disorder is intermediate. Whenever the prognosis is extremely poor or extremely favorable, these factors are not relevant.

effectively treated with three rather than six courses of chemotherapy and consolidated with radiation therapy.

MD Anderson Tumor Score

This system developed in 1988, known as MD Anderson Tumor Score, classifies patients according to prognostic risk. Each adverse variable is assigned one point: Ann Arbor stage (III-IV), symptoms (fever, sweats, weight loss > 10%), tumor bulk (mass > 7 cm or mediastinal mass visible in plain chest film), β-2 microglobulin (50% or > above normal), and LDH (10% or > above normal). It has the advantage that it divides cases into only two groups: those with 0-2 factors who have a cure rate of 83% vs. those with > 2 adverse factors whose cure rate is only 24%. By doing this, it eliminates the any intermediate prognostic categories such as those that result with the IPI. Those with unfavorable tumor scores and particularly when over 60 years, have fared poorly irrespective of treatment regimen used and for these patients new investigational studies are recommendable (11).

Revised International Prognostic Index (R-IPI)

The revised International Prognostic Index (R-IPI) was developed to predict the outcome of individuals receiving Rituximab in combination with CHOP chemotherapy. Since a significant improvement in prognosis occurred with the introduction of Rituximab, the survival results predicted by the IPI changed. The R-IPI score is able to segregate patients into three groups (very good, good, poor), all of whom have survival > 50% in the new era. This newer prognostic index was developed by Sehn, et al. (12). The R-IPI is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP (12).

Prior to Rituximab, the IPI scoring system would have identified the most favorable risk group as "low-risk", with predicted 5-year survival of 73%. According to the R-IPI the predicted 4-year overall survival is now 94%.

For a very useful calculator that will compute the predicted survival of patients with diffuse large B cell lymphoma using the R-IPI, the reader can visit the following website: http://www.qxmd.com/hematology/Hematology-Calculators-Online.php.

Future directions: Gene profiling

Because of the large fraction of cases that fall into the intermediate prognostic categories, the IPI has not proved effective enough in stratifying patients with diffuse large B-cell lymphoma for therapeutic trials. A lot of hope has been placed on the gene expression-based method to serve this purpose (3). Three gene expression subgroups are recognized: germinal center B-cell-like (Figure 1), activated B-cell-like, and type 3 or unclassfied. Additional types that have been recognized include the “lymph node” and the proliferation signatures.

The two most common oncogenic events in diffuse large B-cell lymphoma, bcl-2 translocation and c-rel amplification, were detected only in the germinal-center B-cell-like subgroup. This subgroup has a higher survival rate. The major histocompatibility complex (MHC) class II gene-expression signature correlates with a good outcome, suggesting that antigen presentation to the immune system has a role in chemotherapeutic responses. The genes in the lymph node signature that are associated with a good outcome codify for components of the extracellular matrix and connective-tissue growth factor, a mediator of fibrosis that promotes the synthesis of the matrix. Sclerotic reactions in some diffuse large B-cell lymphomas may reflect these changes. Other genes in the lymph node signature are characteristically expressed in macrophages and natural killer cells, result in the antitumor immune response after chemotherapy and are associated with improved survival. The germinal center B-cell gene expression carries a favorable prognosis perhaps due to decreased activity of the nuclear factor κB signaling pathway. This protective pathway interferes with the apoptotic effect of chemotherapy. In contrast, activated B-cell-like diffuse large B-cell lymphoma is characterized by activation of this pathway, which blocks the apoptosis induced by chemotherapy. DNA microarrays can be used to formulate a molecular predictor for survival after chemotherapy for diffuse large B-cell lymphoma (3).

The findings regarding the prognostic implications of gene profiling, however have not been totally consistent in all studies. Some studies have shown contradictory findings. Perhaps the most important application of this technique will be in identifying new therapeutic targets. A good example of this application is the discovery by Shipp et al of the overexpression of Protein Kinase C-b (PKC-b) in many cases of DLCL by using gene profiling techniques. Activation of PKC-b has been implicated in tumor-induced angiogenesis as well as tumor cell proliferation, anti-apoptosis, and tumor invasiveness. PKC-b is associated with an unfavorable outcome and a new drug, Enzastaurin, has been shown to inhibit PKC-b. This drug is undergoing intensive investigation in patients with unfavorable prognosis once they complete treatment with CHOP-R.

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