Can we improve upon the International Index?

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Summary

The heterogeneity in outcomes in aggressive non-Hodgkin’s lymphoma has prompted the development of clinical prognostic factor models which identify patients with different likelihoods of being cured of their disease. However, these clinical prognostic factor models are based on clinical features that are, in large part, surrogate variables for the biological heterogeneity of the disease. This review summarizes the development of clinical prognostic factor models and discusses some of the more recently described cellular and molecular features that may contribute to the biologic heterogeneity of aggressive NHL.

Key words: aggressive non-Hodgkin’s lymphoma, immune response, karyotype, prognosis

Clinical prognostic factors

The aggressive non-Hodgkin’s lymphomas include diffuse large B-cell lymphomas, anaplastic large-cell lymphomas, and a variety of peripheral T-cell lymphomas. The diffuse large B-cell lymphomas include the categories previously defined by the Working Formulation as F (diffuse mixed-cell lymphoma), G (diffuse large-cell lymphoma), and H (immunoblastic large-cell lymphoma) [1].

Until recently, patients with aggressive non-Hodgkin’s lymphomas (NHLs) were staged with the Ann Arbor classification, which was originally developed for Hodgkin’s disease. This schema emphasizes the distribution of nodal disease sites because Hodgkin’s disease commonly spreads via contiguous lymph node groups [2]. Because the patterns of disease spread in Hodgkin’s and NHLs are somewhat different, it is not surprising that the Ann Arbor classification is less accurate in identifying prognostic subgroups of patients with aggressive NHLs. For this reason, investigators have attempted to identify clinical prognostic factors and associated classification schema that more accurately reflect the behavior of these diseases [3].

A variety of pretreatment clinical characteristics have been associated with the survival of patients with aggressive NHLs: age at diagnosis, systemic (B) symptoms, performance status, serum LDH, serum β2-microglobulin, number of nodal and extranodal sites of disease, tumor bulk, and the distinction between localized and advanced-stage disease [3]. These clinical characteristics are thought to reflect the tumor’s growth and invasive potential (lactate dehydrogenase [LDH], β2-microglobulin, stage, mass size, number of nodal and extranodal sites of disease, bone marrow [BM] involvement), the patient’s response to the tumor (performance status, B symptoms), and the patient’s ability to tolerate intensive therapy (performance status, BM involvement, age) [3]. Clinical pretreatment variables have been used to develop prognostic factor models predictive for an individual patient’s risk for death [4-11]. Although the specific clinical features included in these prognostic factor models differed, all models incorporated parameters of disease volume and extent of tumor involvement at presentation.

International Index

To develop a widely accepted prognostic factor model for patients with aggressive NHLs, institutions in the United States, Europe, and Canada recently participated in the International Non-Hodgkin’s Lymphoma Prognostic Factors Project [12]. In this project, patients with aggressive NHLs who were treated with a doxorubicin-containing combination chemotherapy regimen between 1982 and 1987 were evaluated for pretreatment clinical features predictive for overall survival and relapse-free survival [12]. Clinical features that were independently associated with survival included age, LDH, performance status, stage, and number of extranodal disease sites. These features were incorporated into a model that identified groups of patients with different risks for death, the International Index [12]. Since the relative risk associated with each of the clinical features was comparable, an individual patient’s relative risk for death was determined by adding the number of adverse prognostic factors present at diagnosis. The relative risk for death in patients with each possible number of adverse prognostic factors was determined, and groups of patients with similar relative risk (low [L], low-intermediate [L-I], high-intermediate [H-I], or high [H] risk) were identified. In 2031 patients of all ages, the four International Index risk
groups had predicted five-year survivals of 73, 51, 43, and
26%, respectively [12].

Since younger and older patients had significantly
different outcomes and patients ≤ 60 years were more
likely to be candidates for intensive experimental regi-
mens, an age-adjusted model for patients ≤ 60 years of
age (age-adjusted International Index) was also devel-
oped [12]. In 1274 younger patients, the clinical features
that were independently associated with survival included
stage, LDH, and performance status. An age-adjusted
model based on these three features identified four risk
groups of patients ≤ 60 years of age with predicted five-
year survivals of 83, 69, 46, and 32% [12].

Cellular and molecular features associated with prognosis

It is important to recognize that the clinical features
incorporated into predictive models in NHLs are, in
part, surrogate variables for the biological heterogeneity
of these diseases. For example, it is the biological features
associated with having an elevated serum LDH rather
than the elevated LDH itself that adversely affect a
patient’s outcome. In recent years, cellular and molecular
features, including tumor cell proliferation, immunophe-
notype and host immune response, adhesion molecule
expression, and karyotypic abnormalities, have been
linked to survival in NHLs [3]. It is likely that the newly
identified biologic variables will eventually replace clin-
cal surrogate features in prognostic factor models and
form the basis for unique approaches to therapy in
specific subsets of patients.

Tumor cell proliferation

Several methods, including flow cytometric DNA assess-
ment [13] and tritiated thymidine uptake [14], have been
utilized to evaluate tumor cell proliferation and to corre-
late this parameter with long-term survival in patients
with aggressive non-Hodgkin’s lymphoma. Tumor cell
proliferation has also been evaluated in aggressive non-
Hodgkin’s lymphoma using the nuclear proliferation
antigen Ki-67 [15]. In patient groups that were similar in
age, stage, tumor burden, LDH, therapy, and CR rate,
Ki-67 expression was closely correlated with median
survival and was an independent factor in multivariate
analysis [16].

Immunophenotypic characteristics

Although the majority of aggressive non-Hodgkin’s ly-
phomas are of B-cell origin, up to ~ 30% of these tumors
have a peripheral T-cell phenotype. In the largest reported
series of immunophenotyped aggressive lymphomas, 30% of
361 patients had peripheral T-cell disease [17]. These
peripheral T-cell lymphomas included Working Formu-
lation categories of immunoblastic lymphomas (50%),
anaplastic lymphomas (10%), and diffuse mixed lympho-
mas (36%), but no classic large-cell lymphomas [1, 17]. In
contrast, the vast majority of B-cell lymphomas were
classic (WF) large-cell lymphomas (71%), with only small
numbers of immunoblastic lymphomas (15%) or diffuse
mixed-cell lymphomas (11%) [17]. In this series, patients
with peripheral T-cell lymphomas were more likely to
present with advanced-stage disease and B-symptoms,
and to have splenic and skin involvement [17]. Although
the patients with peripheral T-cell lymphomas responded
to standard induction therapy as well as patients with
B-cell disease, the patients with peripheral T-cell lym-
phoma had higher rates of relapse [17]. In earlier small
studies, a larger proportion of peripheral T-cell lympho-
mas fell into the high grade category of the Working
Formulation [18], and peripheral T-cell lymphomas were
more frequently associated with skin involvement and B
symptoms [18, 19].

Host immune response

Recent data from a variety of sources implicate host
immune responses in the development of and reaction
to aggressive non-Hodgkin’s lymphoma. The extremely
biased usage of VH genes in one series of diffuse large-
cell lymphomas prompts speculation regarding the role
of antigen stimulation of specific VH-expressing premalign-
nant clones [20]. Additional studies suggest that patients
with drug-induced or infection-associated immunodefici-
cy have an increased risk of developing aggressive
non-Hodgkin’s lymphoma [21–23].

Since ‘tumor antigens’ may be recognized in association
with major histocompatibility complex (MHC) molecules,
several investigators have postulated that the absence of
MHC-encoded recognition structures could limit host
tumor immunosurveillance in aggressive non-Hodgkin’s
lymphoma. In a small series of large-cell lymphoma
patients stratified for clinical characteristics, patients
whose tumors lacked HLA-DR had significantly shorter
median survivals than patients with HLA-DR+ tumors
(0.5 vs. 2.8 years, P = 0.003) [24]. In a follow-up study,
the tumor expression of class I and class II MHC determi-
nants was correlated with the numbers of CD8+ T-tumor
infiltrating lymphocytes (TIL) in primary tumor speci-
mens [25]. Sixty-eight percent of the tumors with low
CD8+ T-TIL counts were missing one or more class I or
class II HLA determinants, whereas only 20% of tumors
with high CD8+ T-TIL were missing similar MHC deter-
minants (P = 0.0004), prompting speculation that the loss
of tumor MHC molecules might result in low T-TILs [25].

Additional MHC-associated structures such as β2-
microglobulin have also been associated with the prog-
nosis of aggressive NHL. β2-Microglobulin is a small
extracellular protein that is noncovalently associated
with α-chain of the class I MHC gene; the protein is also
detectable in serum. Elevated serum β2-microglobulin
levels are associated with high tumor burdens and short-
ened survival in patients with aggressive NHL. Although
increased serum β2-microglobulin levels have not yet been associated with decreased lymphoma cell surface β2-microglobulin or deficient antitumor responses, serum β2-microglobulin is an easily measured parameter that has been incorporated into a predictive serologic classification system for aggressive NHL [26].

Adhesion molecule expression

The expression of certain cell surface adhesion molecules such as CD44 also has prognostic significance in aggressive NHL [3]. CD44 (lymphocytic homing receptor [LHR], Hermes antigen) facilitates the binding of lymphocytes to high endothelial venules and permits the extravagation of lymphocytes into nodal areas [27]. In early studies, LHR-negative aggressive lymphomas were less likely to disseminate than lymphomas with increased LHR expression [28-31]. In additional studies, 51% of patients with CD44\textsuperscript{high} lymphomas but only 12% of patients with CD44\textsuperscript{low} lymphomas presented with advanced stage disease. Not surprisingly, patients whose tumors had increased levels of CD44 expression also had shorter survivals [30, 31]. These data prompt speculation that this adhesion molecule may promote the dissemination of aggressive lymphomas. In fact, an aggressive lymphoma cell line transfected with the 'hematopoietic' CD44 isoform metastasized more frequently in nude mice than CD44- parental cells [32]. Additional studies also suggest that extranodal and advanced-stage aggressive non-Hodgkin's lymphomas express additional CD44 variants, including an isoform containing an epitope associated with the metastatic spread of epithelial malignancies [33]. Recent studies suggest that the expression of this CD44 variant has independent adverse prognostic significance in aggressive NHL [34].

Karyotypic abnormalities

Several chromosomal abnormalities have been identified in aggressive non-Hodgkin's lymphoma although there is no single karyotypic abnormality that is a hallmark for this disease. Karyotypic abnormalities in general [35, 36] and specific deletions and abnormalities of the short arm of chromosome 17 and 7 have been associated with adverse outcomes in aggressive NHL [37, 38]; abnormalities involving chromosomes 1, 2, 3, 6, 11, 12, 14, and 18 have also been described [35, 36, 39, 40].

A substantial percentage (up to 30%) of aggressive non-Hodgkin's lymphomas also have the t(14;18)(q32;q21) trademark of follicular lymphomas [39, 40]. This chromosomal translocation results in inappropriately elevated levels of the 18q21 gene product, bcl-2 [41-45], which blocks programed cell death (apoptosis) in B lymphocytes [46, 47]. Transgenic mice bearing a bcl-2 immunoglobulin minigene that structurally mimics the t(14;18)(q32;q21) chromosomal translocation developed follicular hyperplasia [48]. In a large percentage of these transgenic animals, the follicular hyperplasia evolved into immunoblastic lymphomas, and in half of these immunoblastic lymphomas, c-myc alleles were rearranged [48]. These data prompt speculation that in certain aggressive non-Hodgkin's lymphomas, tumor progression may be related to the aberrant expression of specific genes that regulate both cell death (bcl-2) and cell growth (c-myc) [48]. Since bcl-2 protein levels were also elevated in aggressive lymphomas without t(14;18)(q32;q21), mechanisms other than chromosomal translocation may also result in pathogenetically relevant bcl-2 overexpression [49]. In a recent series of patients with aggressive non-Hodgkin's lymphoma, increased bcl-2 expression was significantly more common in patients with advanced stage disease; bcl-2 overexpression was also closely linked with reduced disease-free survival (DFS) (bcl-2+ patients vs. bcl-2− or −/+ patients, 60 vs. 82% 3-year DFS; \( P = 0.01 \)) [50]. These observations are of particular interest because bcl-2 overexpression has been associated with reduced chemosensitivity of murine and human lymphoma cell lines to many of the drugs utilized in current lymphoma regimens [51, 52]. In similar studies, the overexpression of a bcl-2 homolog, bcl-x, also reduces the chemosensitivity of lymphoid cell lines to a variety of chemotherapeutic agents [53].

Chromosomal translocations involving 3q27 and several other loci have been identified in 8 to 12% of diffuse lymphomas [54-57]. The gene from the 3q27 breakpoint has been cloned and identified as a putative zinc finger transcription factor, bcl-6. The bcl-6 gene was truncated within its 5' noncoding region in 33% of diffuse LCL samples but was not altered in other lymphoid malignancies such as follicular, Burkitt's, and small lymphocytic lymphomas and acute and chronic lymphocytic leukemias [57]. Bcl-6 transcripts were identified in mature B cells but not pre-B cells, plasma cells, T cells, or other hematopoietic cell types [57], prompting speculation that bcl-6 may be a proto-oncogene that functions to control normal B-cell differentiation and specifically contributes to the pathogenesis of diffuse large B-cell lymphoma. The rearrangement of bcl-6 has been shown to have prognostic significance in aggressive NHL. In a series of 102 patients with aggressive NHL, 23 had bcl-6 rearrangements that were detectable by Southern blot [58]. Although patients with bcl-6 rearrangements were also more likely to present with extranodal disease, these patients were more likely to remain free from progressive disease than patients with germline bcl-6 [58]. Furthermore, bcl-6 status had independent prognostic significance in this series of patients.

Additional karyotypic abnormalities including deletion of the pl5/p16 cyclin dependent kinase inhibitors [59, 60] and amplification of the rel proto-oncogene [61] have also been identified in subsets of aggressive NHLs.

Conclusion

As the above-mentioned cellular and molecular parameters and newly identified biological features are evaluated
in larger numbers of patients with aggressive non-Hodgkin's lymphoma, the biological heterogeneity of this disease will be better appreciated. Already, certain biologic variables have been linked with known clinical prognostic factors [62]. Other cellular and molecular features have been shown to have independent prognostic significance (Table 1). Still other features have not yet been examined for their relationship to known clinical variables. With a more complete understanding of aggressive NHL, it is likely that we will substitute biologic variables for clinical surrogate features in our prognostic factor models and target these biologic variables for therapy in specific subsets of patients. In the meantime, widely accepted clinical models such as the International Index and the age-adjusted Index will aid in the identification of specific patient risk groups and the ongoing comparison of different therapeutic approaches.

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