

Revisão / Review

Risk stratification for indolent lymphomas

Estratificação de risco dos linfomas indolentes

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Indolent B-cell lymphomas account for approximately 40% of all non-Hodgkin lymphomas (NHLs). Advances in technology have contributed to improvements in the diagnosis and classification of indolent non-Hodgkin lymphomas. Follicular Lymphomas are the most common although the frequency varies significantly throughout the world. The description of the Follicular Lymphoma International Prognostic Index (FLIPI) was an important step in identifying patient subgroups, but its use in the clinical practice has not been established yet. The use of a larger number of paraffin active monoclonal antibodies for immunohistochemistry, molecular cytogenetic studies including standard cytogenetics, multi-color fluorescence in-situ hybridization (FISH), polymerase chain reaction and locus-specific fluorescence in-situ hybridization as well as developments in high-resolution techniques including microarray gene expression profiling allow more accurate diagnosis and precise definition of biomarkers of value in risk stratification. The identification of disease-specific gene lists resulting from expression profiling provides a number of potential protein targets that can be validated using immunohistochemistry. Analyses of gene expression profiles or constitutive gene variations may also provide additional insight for prognostication in the near future. A comprehensive understanding of the biology of these distinct lymphoid tumors will allow us to identify novel disease-related genes and should facilitate the development of improved diagnosis, outcome prediction, and personalized approaches to treatment.

Keywords: Lymphoma, non-Hodgkin; Prognosis; Treatment outcome; Biologic markers; Lymphoma, B-cell; Lymphoma, follicular/pathology

Introduction

One of the main treatment strategies in the management of cancer patients is to focus on the individual. In respect to oncology, diseases labeled under the same name present extremely heterogeneous and even unpredictable biological behavior. The patient's response to disease also varies according to the genotype or phenotype.

In developing countries like Brazil, the social-economic aspect should also be taken into account when approaching

the patient as it may greatly interfere with adherence and coping with therapy. Many patients live in distant places and have no clinical support when complications related to aggressive chemotherapy occur. Similarly, it is important to check whether there are sufficient hospital beds when these complications are detected.

An individual approach to treatment is more desirable when using clinical and biological risk predictors that have previously been tested in broader multi-center studies. Cancer itself involves biological factors that have been analyzed in

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Conflito de interesse: sem conflito de interesse

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respect to response and survival, although what is known is just the tip of the iceberg. The best approach is to study, learn and, above all, apply our knowledge about biological factors to the individual patient.

Clinical predictors allow a thorough analysis of the patient's body functioning and nutrition status which can interfere in responsiveness to certain drugs and protocols. Poorly rated patients are less likely to be submitted to aggressive protocols as they are more prone to liver, bladder, heart, neuron and bone marrow diseases or infectious toxicity. Patients suffering from neuron or heart disease may not tolerate curative treatment and, thus, the adopted treatment is often merely palliative. Poorly rated patients in respect to the functional conditions of the tumor can first be treated more cautiously and, as the clinical status of the patient improves, they may receive curative treatment.

All these observations apply to non-Hodgkin lymphomas (NHLs), which are a heterogeneous group divided into indolent, aggressive and highly aggressive depending on the clinical, immunophenotypic, genetic and molecular features.

Prognostic clinical factors are undoubtedly easier to follow and should be used regularly. However, the advent of gene expression or gene signature techniques helps to improve the understanding and stratification of these groups.

We previously reviewed aggressive lymphomas and will herein review indolent lymphomas, formerly coined low-malignant lymphomas.

The so-called indolent lymphomas present slow development as a result of low cell proliferation rates as opposed to aggressive lymphomas which have moderate cell proliferation.

Although there is a variation in geographic incidence, indolent lymphomas account for 40% of NHL.⁽¹⁾ B-lymphoid diseases are predominant in this group, with follicular lymphomas (FL) being the most common.⁽²⁾ (Table 1).

Table 1. Frequency of indolent lymphoma

	Frequency (%)
Follicular Lymphoma Grade 1-3A	22
Mucosa-associated lymphoma	6
Lymphoplasmacytic lymphoma	5
Lymphocytic lymphoma	1
Nodal marginal zone lymphoma	1

Identifying risk subgroups in the case of indolent lymphomas is a difficult clinical matter. The questions about which advanced stage patients should receive early treatment and which factors make it easier for histological changes to take place remain unclear.

Follicular lymphoma

Follicular lymphomas originate in germinal center B cells (GC)⁽³⁾ with most patients being diagnosed in the advanced stage. They cannot be cured using conventional treatment and show a median survival of 8 to 10 years. Nevertheless, with the advent of chemotherapy, mortality rates in the first years have been significantly reduced. Relapse is still observed and every year about 2% of the cases become highly-aggressive lymphomas, thus associated to a worse prognosis.⁽⁴⁻⁸⁾

Biological and molecular risk factors

Follicular lymphomas are a chronic lymphoproliferative B-phenotype-like disease (CD19, CD20, CD22 surface immunoglobulin) positive for CD10 and Bcl-6 antigens. It can be classified as grade 1 (<5 centroblasts), grade 2 (6-15 centroblasts), grade 3a (> 15 centroblasts + centrocytes) and grade 3b (arrays of centroblasts) but without demonstrating any relevant prognostic significance. Subtype 3b is closer to activated B-cell diffuse large B-cell lymphoma (DLBCL) than the other FL subgroups.⁽⁹⁾

About 80-90% of FL show t (14;18) (q31;21) which results in IGH-BCL2 gene fusion and over-expression of the anti-apoptotic protein Bcl-2.⁽¹⁰⁾ The breaking point of the BCL2 gene does not seem to show prognostic impact. Secondary genetic abnormalities often occur in FL hence contributing to worse or better prognoses. For example, 6q23-26 and 17p abnormalities result in loss of tumor-suppressor genes and are correlated to worse prognoses and +7 and +18 abnormalities are associated with better prognoses.⁽¹¹⁻¹³⁾

In the persistence of a minimum residual disease as determined by molecular biology, t (14;18) with BCL2 gene rearrangement has been shown to be a relevant prognostic factor after autologous bone marrow transplantation. Eighty-eight percent of relapse cases occur in patients without molecular remission and only 8% of relapse cases occur in patients with negative polymerase chain reaction (PCR) (P < 0.005). However, 70% of patients show molecular remission during maintenance treatment with rituximab.⁽¹⁴⁾

The microenvironment of FL is made up of a mixture of malignant cells, including T lymphocytes and dendritic cells. The number of macrophages in this environment is associated to the prognosis, i.e., patients with < 15 macrophages/field have a median survival time of 16.3 years, whereas patients with > 15 macrophages/field survival time is less than five years. STAT1 gene expression, responsible for interferon-mediated response and for the regulation of macrophage function is also correlated to the prognosis.⁽¹⁵⁾

Studies on gene expression have shown that the predominance of genes related to monocytes and dendritic cells, which are characterized as Type-2 immune response (TLR5, FCGR1A, SEPT10, LGMN, C3AR1), are related to a

worse prognosis in this environment. On the other hand, the predominance of Type-1 immune response associated with activated T-lymphocytes (CD7, CD8B, ITK, LEF1, STAT4) is related to a better prognosis.⁽¹⁶⁾ Changing into highly-aggressive lymphomas is strongly correlated to a reduction of regulating T lymphocytes and the break up of the macrophage network. IL-8, IL-12B, IL-2 and IL-1RN are also associated with the prognosis (P = 0.0001).⁽¹⁷⁾ Thus, the type of immune response in the tumor environment is directly related to prognosis of FL patients. Survival correlates to the clinical prognostic criteria (P < 0.001) implying that the evolution of LF depends on the interaction between malignant cells and a non-neoplastic environment.

Clinical risk factors

The International Prognostic Index (IPI) applied to diffuse large B-cell lymphoma (DLBCL) has not proved suitable for FL.⁽¹⁸⁻²²⁾ By using retrospective studies of independent risk factors that have an impact on survival rates of FL and indolent NHL patients, we did not find an index that would adequately assess the prognosis.^(23,24)

For this sub-group of patients an international prognostic index was established for follicular lymphoma (FLIPI) and validated in a retrospective multicenter study comprising over 4,000 patients.⁽²⁵⁾ This index is also valid for patients treated with anti-CD20 monoclonal antibodies.⁽²⁶⁾ FLIPI considers age, Ann Arbor's stage, the number of impaired lymph node sites, hemoglobin and LDH (Lactate dehydrogenase) to categorize patients in low risk (0-1 point), intermediate risk (2 points) and high risk groups (> 3 points)⁽²⁵⁾ (Tables 2 and 3).

This prognostic index helps both the treatment and follow-up of follicular lymphoma patients. Patients with survival expectancy of more than 70% over 10 years should be treated with less aggressive regimens, whereas high risk

Table 2. Risk factors for Follicular Lymphoma International Prognostic Index (FLIPI)

Variable	Adversity	Points
Age	≥ 60 a	1
Ann Arbor's Stage	III and IV	1
Hemoglobin	< 12.0	1
Lactate dehydrogenase	> upper limit	1
Lymph node sites	> 4	1

Table 3. Risk groups and overall survival according to Follicular Lymphoma International Prognostic Index (FLIPI)

Risk	Low	Intermediate	High
Points	0 -1	2	> 3
OS % 5 years	90.6	77.6	52.5
OS % 10 years	70.7	50.9	35.5

OS = Overall Survival

patients should receive more aggressive or even experimental protocols.⁽¹⁷⁻³²⁾

In spite of being reproducible, FLIPI distinguishes only 17% of the under 60-year-old high-risk patients. Similarly, there are cases for which treatment is prescribed, for example, young patients ranked at Ann Arbor stage I or II with bulky disease, who can be classified as low-risk patients, whereas some elderly patients with spread disease and no treatment prescribed can be classified as high-risk patients.⁽³³⁾ Hence, other risk stratification methods are needed, especially for young individuals. Fluorodeoxyglucose positron emission tomography (PET-FDG) is part of the prognostic investigation of aggressive lymphomas and Hodgkin's lymphomas (HL).⁽¹⁹⁾ Few studies are found in the literature addressing the role of PET-FDG in follicular lymphoma. Zinzani et al. showed an increased progression-free survival over two years for patients with negative PET-FDG at the end of induction therapy.⁽³⁴⁾ Future guidelines for treatment will probably be based on clinical staging systems, genetic profiles and immune response signatures, but these factors do not help us to decide who should have immediate therapy.

Mucosa-associated extralymphonodal lymphoma of lymphoid tissue

Mucosa-associated lymphoid tissue-derived lymphomas (MALTs) usually originate from organs lacking organized lymphoid tissue as a result of persistent antigen stimulation. They account for 7 to 8% of NHL and have been found in different sites such as salivary glands, thyroid, ocular adnexa, breast, lung, skin and liver. As they are rare, prognostic studies are based on retrospective analyses with few cases and heterogeneous therapies making validation of results difficult.

As they are more common, Gastric lymphomas appear to be an exception. They have a slow progression, remain localized for a long time and respond quite well to radiotherapy. Although they may involve extralymphonodal areas at diagnosis, advanced Ann Arbor's stage does not seem to result in worse prognosis.^(35,36) In less than 15% of cases, these lymphomas have adverse prognostic factors, including increased LDH. When compared in regards to their location, non-gastric MALT lymphomas tend to show more frequent relapse and also lower disease-free survival⁽³⁷⁾ compared to gastric MALT lymphomas, despite their high complete remission rates. Due to its more frequent occurrence in the stomach, MALT lymphoma is undoubtedly the most studied. Since *Helicobacter pylori* was recognized as an etiological agent of gastric MALT lymphoma, several works have demonstrated complete remission with only antibiotic therapy.⁽³⁸⁻⁴²⁾ However, some prognostic variables are related to the failure to respond to the eradication of this bacteria, for example, histological and cytogenetic aspects and the site involvement pattern of the tumor.

The change evolution from gastric MALT lymphoma to aggressive lymphoma is not as clear compared to other indolent lymphomas with lymphonodal origins, such as FL and chronic lymphocytic leukemia (CLL). The clinical relevance of histological studies was demonstrated in works which split patients into four different sub-groups of MALT lymphoma according to the presence or absence of areas of large lymphoid cells.

Nevertheless, the low reproducibility of the morphological criteria adopted in this study does not allow the clinical application of this prognosis.^(43,44) In spite of this, remission with the eradication of *Helicobacter pylori* in DLBCL is found in a few reports. The invading pattern of the stomach wall evidenced by means of endoscopic ultrasonography is an important prognostic factor to achieve bacterial eradication response.⁽⁴⁵⁻⁴⁷⁾ Hence, endoscopic ultrasonography features can predict the chance of cure with eradication of *Helicobacter pylori*. In a multicenter study of 44 patients selected for antibiotic treatment, a French group studying digestive lymphoma showed that higher response rates (78%) were found in cases in which only the mucosa was affected. When the sub-mucosa area, either muscles or serosa, was affected response rates were 43%, 20% and 25%, respectively. None of the patients with perigastric lymphadenopathy responded to treatment to eradicate the bacteria.⁽⁴⁸⁾

Another adverse prognostic factor related to the eradication of *Helicobacter pylori* is the presence of t(11;18). In a group of patients with localized gastric lymphoma, the AP12-MLT hybrid gene was found in 9 (75%) of 12 patients who did not respond to antibiotic treatment. This hybrid gene was not observed in any of the 10 responding patients. Even in early Ann Arbor's stage, patients with t(11;18) did not respond to treatment to eradicate the bacteria.⁽⁴⁹⁾

Small lymphocytic lymphoma

Small lymphocytic lymphoma (SLL) is an unusual lymphoma that accounts for 1% to 2% of NHL with pathological features identical to chronic lymphocytic leukemia (CLL). Little is known about this lymphoma as most patients present with bone marrow and peripheral blood involvement and few of them present restricted nodal disease.

Most of the prognostic studies are performed on CLL patients and several adverse factors, such as diffuse bone marrow (BM) involvement, 17 p deletions, 11 q deletions, complex karyotypes, mutated IGH genes and CD38 expression were studied for CLL with some also being used for SLL; t(14;19) does not often occur in SLL but when it does it shows more aggressiveness.⁽⁵⁰⁾ In CLL, changes such as 17 p deletions and 11q deletions are associated to a worse prognosis.⁽⁵¹⁾ Nowadays, as both immunohistochemistry and immunophenotyping are easy to perform, ZAP-70 expression

shows good correlation with the non-mutant IGH gene, although it does not correlate well with the CD38 expression.⁽⁵²⁾ Other genes are found to correlate with prognosis, such as lipoprotein lipase (*LPL*) and disintegrin-metalloprotease 29 (*ADAM29*) which are over-expressed in mutated and unmutated SLL, respectively.⁽⁵³⁾

Serum markers, such as β -2 microglobulin, have just been analysed in relation to progression-free survival, especially in the initial stages.⁽⁵⁴⁾

In practice, these factors should not be used to guide treatment, even though patients with 17p deletions do not respond to alkylating agents or to fludarabine.

Non-MALT marginal zone lymphomas

Marginal zone lymphomas (MZL) have been found in lymphoid tissue, spleen and lymph nodes, and in the mucous membranes (MALT). The International Group of Studies on Lymphoma has identified three types of MZL lymphomas: extranodal MALT lymphoma, MZL splenic lymphoma (with or without villous lymphocytes) and nodal MZL lymphoma.

Due to its rare occurrence and difficult diagnosis, few data are found in regards to clinical and prognostic markers for non-MALT MZL.

Splenic MZL patients show longer survival in most series with survival rates of over 50% over five years being reported. Lymphonodal and extralymphonodal progression may occur at approximately 3.7 years after diagnosis or transformation into DLBCL in between 12 and 85 months from the development of the disease. The change is often associated with p 53 inactivation or other chromosomal abnormalities. Although some studies have shown a connection between high LDH and IPI with prognosis in this kind of lymphoma, this does not seem to be suitable for the prognosis, as no other criteria influence its development. Other factors described as adverse prognosis are the number of leukocytes over 30 or 20 x 10⁹ and lymphocytes < 4 or > 20 x 10⁹, high β -2 microglobulin, presence of monoclonal components, anemia, low albumin and initial chemotherapy, besides CD38 expression and unmutated IGH gene.⁽⁵⁵⁾

The prognosis of nodal MZL is similar to that of splenic MZL patients and worse than of MALT lymphoma patients. Overall survival is between 50-70% over five years. Due to the small number of reported cases, specific prognostic factors are not known with nodal involvement being predominant among relapse cases.^(55,56)

Lymphoplasmacytic lymphoma

Lymphoplasmacytic lymphoma is also a rare type of lymphoma which accounts for only 1.2% of NHL and, for this, it is little studied. It often involves lymph nodes and

bone marrow, although it shows little manifestation in peripheral blood cells. The morphology and immunohistochemistry are very similar to those of plasmacytes, with no CD19, CD20 and CD5 expression. In most cases, IgM monoclonal protein is found in the blood or urine. There are no consistent clinical studies which assign risk factors to this kind of lymphoma. Although the presence of t(9;14)(p13;q32) has been related to lymphoplasmacytic lymphoma, this correlation has not been confirmed.⁽⁵⁶⁾

Resumo

Os linfomas de células B indolentes representam aproximadamente 40% do total de linfomas não Hodgkin (LNHs). O avanço das tecnologias novas tem contribuído para a melhora no diagnóstico e classificação dos LNH indolentes. O linfoma folicular é o mais comum e sua frequência varia significativamente pelo mundo. A descrição do Índice Internacional de Prognóstico dos linfomas folicular (FLIPI) representa um passo importante na identificação de subgrupos de pacientes, mas seu uso na prática clínica ainda necessita ser estabelecido. O uso de um número maior de anticorpos monoclonais para imunoistoquímica, estudo citogenético incluindo citogenética convencional ou hibridização in-situ por fluorescência (FISH), bem como o desenvolvimento de técnicas de alta resolução incluindo a expressão por microarray possibilita maior acurácia no diagnóstico e definição precisa dos biomarcadores com valor na estratificação de risco. A identificação de genes específicos para os diversos tipos de linfomas permite o reconhecimento de potenciais proteínas alvo que podem ser validadas usando imunoistoquímica. Análises da expressão do perfil de genes ou variações genéticas constitutivas pode também prover conhecimentos adicionais para o prognóstico em um futuro próximo. Um entendimento da biologia desses distintos tumores linfoides permite-nos identificar novos grupos de genes relacionados à doença e deve facilitar o desenvolvimento diagnóstico, predizendo a evolução e permitindo tratamentos personalizados.

Descritores: Linfoma não Hodgkin; Prognóstico; Resultado de tratamento; Marcadores biológicos; Linfoma de células B; Linfoma folicular/patologia

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