BACKGROUND INFORMATION ON NON-HODGKIN'S LYMPHOMA

General

Non-Hodgkin's lymphomas (NHLs) encompass several unique malignant lymphoid disease entities that vary in clinical behavior, morphologic appearance, immunologic, and molecular phenotype. The various types represent neoplastic lymphoid cells arrested at different stages of normal differentiation. Based on their natural history, NHLs can be clinically classified as indolent, aggressive, and highly aggressive.

Epidemiology

NHLs are the fifth most common cause of cancer in the United States, with an estimated incidence of 63,600 cases in 2001[i]. Follicular center cell lymphomas are the second most common subtype, comprising approximately 40% of all non-Hodgkin's lymphomas. Since 1950, the incidence of NHL has steadily increased at approximately 4% per year.

Classification

Several histologic classifications of NHLs exist. Commonly used systems are the 1982 International Working Formulation (IWF)[ii] and the 1994 Revised European-American (REAL) classifications[iii]. These classification systems group lymphoid neoplasms according to clinical behavior (low grade/indolent, intermediate grade/aggressive, or high grade/very aggressive). Historically, this grouping often served as a basis for choosing a first line therapy.

IWF and REAL Classification by Proposed Clinical Grouping

IWF	REAL
Low Grade Lymphomas	Indolent (low-risk) lymphoma
Small lymphocytic (A)	Small lymphocytic
Follicular small cleaved (B)	Lymphoplasmacytic
Follicular mixed (C)	Marginal zone
	Splenic
	MALT B-cell (extranodal)
	Monocytoid B-cell (nodal)
Intermediate-grade lymphomas	Follicule center, small grade I
Follicular large (D)	Follicule center, mixed small/large grade II
Diffuse small cleaved (E)	
Diffuse mixed (F)	Aggressive (intermediate-risk) lymphomas
Diffuse large cell (G)	Mantle cell
	Follicule center, large grade III
High grade lymphoma	Diffuse large B-cell
Immunoblastic; large cell (H)	Primary mediastinal (thymic), large B-cell
Lymphoblastic convoluted and nonconvoluted (I)	Burkitt-like, high grade B-cell
Lymphoblastic small noncleaved (J)	Very Aggressive (high risk) lymphomas
	Precursor B-lymphoblastic
	Burkitt's

More recently, the World Health Organization (WHO) proposed a new classification system [iv]. Unlike the IWF and REAL classifications, the WHO committee felt that

grouping lymphoid neoplasms according to clinical behavior was neither necessary nor desirable[v]. The committee recognized that specific disease entities could be defined by a combination of morphology, immunology, genetic features, and clinical features. Each entity had distinct clinical behavior and outcome predictable by applicable prognostic factors (e.g.; the international Prognostic Index) and related to the type of initial therapy administered. The committee concluded that each lymphoma type needed to be treated as distinct entities. Therefore, rather than depending on clinical grouping (i.e.; low grade/indolent, etc.), the committee emphasized that clinical decisions should be based on the specific lymphoid neoplasm.

Proposed WHO Classification of B-Cell Neoplams

- Precursor B-cell neoplasm
  - Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)
- Mature (peripheral) B-cell neoplasms*
  - B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
  - B-cell prolymphocytic leukemia
  - Lymphoplasmacytic lymphoma
  - Splenic marginal zone B-cell lymphoma (1/2 villous lymphocytes)
  - Hairy cell leukemia
  - Plasma cell myeloma/plasmacytoma
  - Extranodal marginal zone B-cell lymphoma of MALT type
  - Nodal marginal zone B-cell lymphoma (1/2 monocytoid B cells)
  - Follicular lymphoma
  - Mantle-cell lymphoma
  - Diffuse large B-cell lymphoma
    - Mediastinal large B-cell lymphoma
    - Primary effusion lymphoma
  - Burkitt's lymphoma/Burkitt cell leukemia

Natural History

The median age prevalence of indolent lymphoma is in the sixth decade. B-cell indolent (low-risk group) NHL is not curable with standard treatment. First line therapy is commonly associated with a high rate of clinical response followed by relapse. Subsequent remissions may occur but at a progressively lower rate and with progressively shorter durations with a median progression-free survival (PFS) frequently less than 6 months[vi] using traditional chemotherapeutic regimens. However, recent studies suggest that treatment using unconjugated monoclonal antibodies directed against CD20 antigen may yield a prolonged median PFS greater than 6 months[vii] in relapsed or refractory indolent NHL populations.

Over time, indolent NHL may transform to aggressive (intermediate risk) or very aggressive (high-risk) lymphomas that have a more aggressive clinical course. The incidence of transformation ranges from 40% to 70% and is associated with disease progression and known adverse prognostic factors[viii]. In general, transformation has a poor prognosis and frequently results in a rapidly fatal outcome. However, some patients can have complete responses to salvage chemotherapy regimens and achieve durable complete remissions[ix]. Overall survival following transformation is poor with an estimated median survival ranging from 7 to 22 months.

Prognostic Indicators

The most valuable and widely used prognostic indicator system for NHL is the International Prognostic Index (IPI)[x]. The IPI is a prognostic index that was developed to predict outcome in patients with aggressive NHL, based on patients' clinical characteristics before treatment. However, the IPI has been shown to apply to indolent (low-risk) lymphoma[xi].

International Prognostic Index

The Tumor Score system divides the population into two risk groups by assigning one point for the presence of each of five variables:

- Age (less than or equal to 60 vs. >60 years),
- Tumor stage (stage I or II [localized disease] vs. stage III or IV [advanced disease]),
- Number of extranodal sites of disease (less than or equal to 1 vs. >1),
- Performance status (0 or 1 vs. greater than or equal to 2),
- Serum LDH level (less than or equal to 1 times normal vs. >1 times normal)

Patients with scores of < 1are low risk; 2 low-intermediate risk; 3 high-intermediate risk; and > 3 high risk.

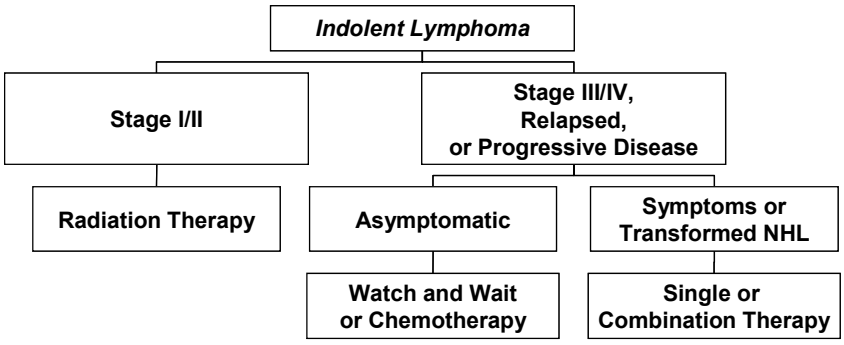
IPI Score and Clinical Outcome (Follicle Center Cell NHL)

IPI	CR (%)	5-yr FFS (%)	5-yr OS (%)	Median OS (mo)
Low	92	75	85	160
Low-Int	81	64	69	108
High-Int	77	38	28	35
High	0	0	0	12

Cytogenetics, gene rearrangement, and oncoproteins are important molecular markers of histologic subtype and mechanisms of lymphomagenesis. BCL2 oncogene (t14;18) overexpression is characteristic of follicular center cell NHLs. However, the use of biomarkers to predict clinical outcome in indolent NHL is investigational and need to be validated in prospective trials.

Therapy
First Line Treatment

Treatment Strategy



Localized indolent lymphoma at initial presentation is unusual and represents less than 5% of the population. Patients with early-stage indolent lymphomas are potentially curable with radiation therapy (46% to 68% 10-year DFS[xii, xiii, xiv]. The addition of chemotherapy to radiotherapy as primary treatment has not convincingly prolonged remission duration or survival.

The majority of patients with indolent NHL present with advanced disease. For the majority of patients, selection of initial treatment is based on the clinical situation, prognostic indicators, physician bias, and patient choice. There is no single standard initial therapy for indolent NHL.

FDA Approved Drugs in NHL
BCNU
Blenoxane
Leukeran
Velban
Oncovin
Cytoxan
Adriamycin
Methotrexate
Intron A
Rituxan

In general, alkylating agents are useful palliative treatment options that can result in improved well-being for most patients, often for long periods. Although commonly used, combinations of chemotherapy have not convincingly resulted in longer or greater number remissions. There is no proof that initial combination chemotherapy will prolong survival in comparison with single drugs. The addition of interferon to initial combination chemotherapy may increase the response rate, significantly prolong remission duration, but prolonged survival has not been unequivocally proven. In the absence of disease-related symptoms, treatment can safely be deferred without adversely impacting survival.

Distinguishing follicular lymphoma into those with predominantly small cells (follicule small, grade I), those with an intermediate number of small and large cells (follicule center, mixed small/large grade II), and those with more large cells (Follicule center, large grade III) is difficult[xv]. However studies that have assessed the clinical behavior or these lymphomas have shown that patients with follicular large cell lymphoma have a shorter remission duration and overall survival than patients with the other subtypes. For these patients, the incorporation of an anthracycline into the initial treatment regimen appears to improve outcome[xvi].

Overall response rates to therapy for low-grade lymphomas at the later stages (Stage III or IV) are between 80% to 90% with different chemotherapeutic regimens. The rate of complete response to initial therapy ranges from 23% to 83% in various studies. The median duration of response for therapy is 2 years for most studies. Less than 10% of patients remain in remission for more than 5 years. However, median survival exceeds 9 years in many series. The choice for either (a) a conservative approach or (b) an aggressive approach exists because there is still no evidence that one is more effective than the other in terms of overall survival.

Commonly Used First Line Treatment of Indolent NHL

Watch and wait
Radiation
- **Localized**
- **Low-dose total body Irradiation**

Oral alkylating agents
CVP
CHOP
CHOP + Rituxan
Mitoxantrone
Second and third generation anthracycline-based regimens
Fludarabine
Cladribine
Transplantation
Interferon alpha-2b

Second Line Treatment

Patients with relapsed indolent lymphoma may repeatedly respond to alkylating agents or combinations containing an alkylating agent, although the proportion responding decreases with each relapse. Patients relapsing after or who are refractory to treatment with alkylating agents often respond to treatment with combinations containing an anthracycline. Responses are also often seen in patients treated with purine analogues alone or in combination with other drugs. High dose chemotherapy followed by autologous or allogeneic reestablishment of bone marrow function can induce long-term remissions but it is not proven whether they are more frequent or of longer duration than with conventionally dosed therapy. The impact of the novel treatment strategies including high-dose therapy on overall survival is still uncertain.

Recent Regulatory Approvals

There are two agents who have received marketing approval for the treatment of relapsed and refractory, low grade NHL. They are Rituxan (Rituximab) and the Zevalin therapeutic regimen. Rituxan is a chimeric monoclonal antibody directed against the CD20 antigen. The Zevalin therapeutic regimen, which is a two stage treatment involving administration of Rituxan plus ibritumomab (a murine monoclonal antibody directed against the CD20 antigen) labeled with 111-Indium, followed one week later by Rituxan plus ibritumomab (a murine monoclonal antibody directed against the CD20 antigen) labeled with 90-Yttrium.

Rituxan is indicated for the treatment of relapsed or refractory, low grade or follicular NHL. Marketing approval was based on 3 single arm trials with a total of 242 registered participants. The ORR was 48% (6% CR and 42% PR) and the median duration of response ranged from 10-12 months. Serious adverse events were uncommon (<5%). In addition, the toxicity profile of Rituxan was mild, dominated by infusional toxicity most notable on the first dose and grade 3 or 4 toxicity occurring in less than 5% of the study population. Based on the very favorable toxicity profile indicating that Rituxan would be very unlikely to impair survival, the BRMAC recommended standard approval of Rituxan.

Zevalin was licensed in Feb. 19, 2002 based upon the results of two efficacy trials conducted in related populations. The first study was conducted in 143 patients with heavily pretreated low-grade follicular NHL, with or without transformation, in which patients were randomized to Rituxan or Zevalin. The results of this study showed a significantly higher response rate for Zevalin (73% vs. 47%), higher complete response rates (20% vs. 9%) and similar durations of response (14.2 vs. 12.1 mos) and times-to-progression (11.2 vs. 10.1 mos), as determined by an masked, independent review panel. There was also substantially greater hematologic toxicity for Zevalin-treated patients. The ODAC recommended accelerated approval for Zevalin in this population based upon the surrogate endpoint of higher response rate but felt that full approval would require additional data to establish the overall risks and benefits of Zevalin as compared to Rituxan. A confirmatory trial will be conducted to establish the superiority of Zevalin (over Rituxan) on progression-free survival.

The second efficacy study was a single arm trial conducted in 57 patients, 52 of whom had follicular NHL, who were refractory to prior Rituxan. In the subset of 52 patients, the overall response rate to Zevalin was 58% (95% CI 43%, 71%) with a median duration of response of 7.7 months months. Toxicity in this population was qualitatively and quantitatively similar to that observed in randomized study. Based upon the anti-tumor activity in the Rituxan-refractory population together with the information absence of impairment in survival in the Rituxan-controlled study, the ODAC considered the risk-benefit ratio to have been adequately addressed for this patient population and recommended full approval. Zevalin received standard approval for treatment of follicular NHL that had relapsed from or was refractory to standard therapy, including Rituxan. Zevalin received accelerated approval for treatment of treatment of follicular or low grade NHL, with or without transformation, that had relapsed from or was refractory to standard chemotherapy but no prior Rituxan.

[i] http://seer.cancer.gov/Publications/CSR1973_1998/

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