

# Therapy of Aggressive Lymphoma

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In much of the world, non-Hodgkin's lymphomas are increasing in frequency. In the United States, approximately 60,000 cases will be diagnosed this year. The explanation for the rising incidence of non-Hodgkin's lymphoma is not known. However, there have been numerous advances in our understanding of the biology of the disorder, our ability to classify them as specific diseases, and our knowledge about their management.

## Classification of non-Hodgkin's Lymphoma

Unlike the related disorder Hodgkin's disease, non-Hodgkin's lymphoma has a firmly established cellular origin with morphologic subtypes corresponding to various stages of lymphocyte differentiation. The specific diagnosis should be based on the evaluation of an adequate biopsy specimen by an experienced hematopathologist who has access to immunophenotyping, genetic studies, and clinical information. Some types of non-Hodgkin's lymphoma (e.g., follicular lymphoma, MALT lymphoma, and small lymphocytic lymphoma) can be diagnosed based on morphologic information alone.<sup>1</sup> Other types of non-Hodgkin's lymphoma (e.g., T-cell lymphoma, diffuse large B-cell lymphoma, and mantle cell lymphoma) require immunophenotypic studies to be confident of the diagnosis.<sup>1</sup> Finally, mediastinal diffuse large B-cell lymphoma can only be diagnosed when clinical information is available.<sup>1</sup>

The Revised European-American Lymphoma Classification (REAL classification) made it possible to classify non-Hodgkin's lymphomas in clinically relevant subgroups taking into account morphological, biological, and clinical data. This classification is presented in **Table 1**. In a clinical test, this system was shown to be more reproducible than previous systems, and the entities included in the classification were shown to be clinically relevant.<sup>1</sup> The rela-

Table 1. Modified REAL Classification

Precursor Cell Disorders	
B-Cell	T-Cell
Lymphoblastic	Lymphoblastic
Mature or Peripheral Cell Disorders	
B-Cell	T-Cell
Small lymphocytic (CLL)	Mycosis fungoides/Sézary's
Lymphoplasmacytic	Peripheral T-cell, NOS
Marginal zone, MALT	AILD-like
Marginal zone, nodal	Angiocentric nasal
Follicular	Intestinal
mantle cell	Gamma-delta
Diffuse large B-cell	Panniculitis-like
Mediastinal large B-cell	Anaplastic large T/null cell
Burkitt's	Adult T-cell lymphoma/leukemia

tive frequencies of these entities are presented in **Table 2**.

To appropriately manage a specific patient with non-Hodgkin's lymphoma requires both clinical and prognostic information as well as the specific morphologic subtype of the lymphoma. The most frequent method for subdividing patients prognostically is the International Prognostic Index (IPI)<sup>2</sup> (**Table 3**). This index predicts survival of patients with all types of non-Hodgkin's lymphoma. Patients with an adverse score in the IPI with follicular lymphoma have a worse survival than patients with a favorable IPI Score with diffuse large B-cell lymphoma. Even so, most reports of patients with aggressive non-Hodgkin's lymphoma focus on patients with diffuse large B-cell lymphoma, peripheral T-cell lymphoma, anaplastic large T/null cell lymphoma, and mantle cell lymphoma.

## Immunophenotypic and Genetic Findings

The subtypes of non-Hodgkin's lymphoma are recognized in part because of unique immunophenotypic and genetic findings. It has become apparent that particular genetic abnormalities are characteristic of certain subtypes of non-Hodgkin's lymphoma. In fact, the recognition of entities such as anaplastic large T/null cell lymphoma and mantle

Table 2. Relative Frequency of NHL Subtypes

Subtype	Percentage of NHL (%)
Diffuse large B-cell lymphoma	31
Follicular lymphoma	22
Small lymphocytic lymphoma	6
Mantle cell lymphoma	6
Peripheral T-cell lymphoma	6
Marginal zone, MALT	5 (8% if cases with admixed diffuse large B-cell are included)
Mediastinal large B-cell	2
Anaplastic large T/null cell	2
Lymphoblastic (T/B)	2
Burkitt-like	2
Marginal zone, nodal	1
Lymphoplasmacytic	1
Burkitt's	<1

Table 3. International Prognostic Index

Adverse Risk Factors	Age > 60
	Reduced performance status
	Ann Arbor stage III or IV
	Multiple (i.e. >1) extranodal sites of lymphoma
	LDH greater than normal

IPI score: Sum of adverse risk factors

Table 4. Immunophenotypic and genetic findings in NHL.

Lymphoma Type	Immunophenotype	Translocation	Percentage of Occurrence	Oncogene Involved
Mantle cell	B	t(11;14)(q13;q32)	70	BCL-1
Follicular	B	t(14;18)(q32;q21)	90	BCL-2
Diffuse large cell, "de novo"	B	t(14;18)(q32;q21)	20	BCL-2
Diffuse large cell, transformed	B	t(14;18)(q32;q21)	100	BCL-2
Diffuse large cell	B	t(3;-)(q27;-)	40	BCL-6
Burkitt's	B	t(8;-)(q24;-)	100	C-MYC
Anaplastic large cell	T	t(2;5)(p23;q35)	80	NPM/ALK
Lymphoplasmacytoid	B	t(9;14)(p13;q32)	50	PAX-5
Small lymphocytic	B	t(17;-)(p13;-)	10	p53

cell lymphoma was finally confirmed by the discovery of consistent genetic abnormalities. In almost all cases, the cytogenetic abnormalities correspond to over expression, under expression, or abnormal expression of specific oncogenes.

**Table 4** lists the major, recurring genetic abnormalities known to occur in patients with non-Hodgkin's lymphoma. Subtypes of lymphoma that are not listed almost certainly have specific genetic mistakes that have not been discovered. Future therapies will probably aim at trying to alter the products of these abnormal genes either quantitatively or qualitatively.

#### Diffuse Large B-Cell Lymphoma and Peripheral T-Cell Lymphoma

The management of patients with diffuse large B-cell lymphoma and peripheral T-cell lymphoma is usually similar. However, patients with peripheral T-cell lymphoma have a worse prognosis than those with diffuse large B-cell lymphoma.<sup>1</sup> Unfortunately, there is no clear evidence that one particular treatment approach is superior in the B- vs. T-cell lymphomas or vice versa. Patients with these highly aggressive lymphomas who present with localized disease (i.e., disease confirmed to one site or two adjacent sites) when the maximum tumor diameter is less than 10 cm (and usually less than 5 cm) and the LDH is not elevated have an excellent outcome. Early studies show that these patients benefit from initiation of treatment with combination chemotherapy<sup>7,4</sup> rather than initial radiotherapy. More recent studies have focused on the potential advantage that adjuvant radiotherapy might provide such patients.<sup>5</sup> The most common chemotherapy regimen utilized to treat patients with aggressive non-Hodgkin's lymphoma is CHOP (**Table 5**). CHOP given for 6-8 treatment cycles can cure a high proportion of patients with localized lymphoma. However, pilot studies suggested that the cure rate might be even higher when adjuvant radiotherapy was utilized. A trial has completed comparing three cycles of CHOP followed by radiotherapy with eight cycles of CHOP. The disease-free survival rate was superior for patients who received combined modality therapy. The cure rate in such series has averaged

approximately 75%.

Reducing the number of CHOP cycles in such patients limits chemotherapy toxicity. In particular, the risk of delayed left ventricular failure in elderly patients provides an advantage for a reduced amount of chemotherapy. Of course, the radiotherapy gives a long-term risk of second malignancies. In younger patients, there might be some circumstances where avoiding radiotherapy would be preferable (e.g., breast radiotherapy in young women). In patients of any age, avoiding radiotherapy to the salivary glands might be chosen because of the long-term morbidity associated with a dry mouth.

Patients with diffuse large B-cell lymphoma and peripheral T-cell lymphoma presenting with bulky localized disease or more widely disseminated disease are treated with chemotherapy alone in most instances. A large randomized trial comparing CHOP with m-BACOD, ProMACE-CytaBOM, and MACOP-B showed no advantage in overall survival or disease-free survival for any of the regimens.<sup>6</sup> This study has unfortunately reduced interest in trying to develop a superior chemotherapy regimen for the treatment of these patients. However, this is a goal that still must be

Table 5. CHOP

Drug	Route	Mg/M <sup>2</sup>	Days Administered
Cyclophosphamide	IV	750	1
Adriamycin*	IV	50	1
Vincristine	IV	1.4**	1
Prednisone	PO	100 (total dose not mg/m <sup>2</sup> )	1-5

Treatment plan: 1. Four cycles @ 21-day intervals and then restage  
 2. If CR, 2 more cycles and stop  
 3. If good PR, 2 more cycles and restage  
 4. If progression or persisting disease after 6 cycles, change regimen

\* Mitoxantrone can be substituted @ 12 mg/m<sup>2</sup>

\*\* usually 2 mg maximum

pursued since the overall cure rate is only 30-50%.

Our usual treatment approach for such patients would utilize a regimen like CHOP given for four cycles. The patient is then restaged to see if a complete remission has been achieved. If the patient is in complete remission, we would then give two more cycles of treatment and discontinue therapy. If the patient has failed to achieve a complete remission after six cycles, we would consider alternate treatment approaches. Of course, treatment would be changed at the moment there was evidence of disease progression.

Patients who present with adverse risk factors (i.e., having two or three of the IPI risk factors) might benefit from adjuvant application of autologous bone marrow transplantation in initial remission. A large trial performed in France showed a superior cure rate for such patients.<sup>7</sup> An Italian study seemed to suggest the same results.<sup>8</sup> Further confirmatory trials are ongoing. However, in practice, patients who present with adverse risk factors often undergo adjuvant autologous transplantation.

Unfortunately, more than half the patients with widespread diffuse large B-cell lymphoma or peripheral T-cell lymphoma are not cured with standard treatment approaches. In these patients, an alternate chemotherapy regimen (often a platinum-based regimen) can be used to try to induce a second remission. Patients who respond to salvage therapy have been demonstrated to benefit from autologous bone marrow transplantation. In a large international trial, patients undergoing transplantation after remission induced by DHAP (dexamethasone, high-dose cytarabine, and cisplatin) had better disease-free survival and overall survival (**Table 6**).<sup>9</sup>

### Anaplastic T/Null Cell Lymphoma

This recently recognized subtype of non-Hodgkin's lymphoma is clinically distinct from other T-cell lymphomas. Patients with this type of lymphoma are young (median age approximately 33 years), predominantly male (69%), express the CD-30 antigen, typically display a specific translocation between chromosomes 2 and 5, and over express the alk protein.<sup>1</sup> While the exact criteria for identifying the most characteristic cases with this disorder have not been defined, it appears that over expression of the alk protein might be the key in determining the prognosis.<sup>10</sup> Patients with anaplastic large T/null cell lymphoma have a better prognosis than other patients with aggressive non-Hodgkin's lymphoma. The five-year overall survival is greater than 70%, with the majority of these patients being cured with their initial treatment. The management of patients with this

disorder usually utilizes the same regimens as utilized for diffuse large B-cell lymphoma.

### Other Subtypes of Aggressive Non-Hodgkin's Lymphoma

Although mantle cell lymphoma is a tumor predominantly of small cells, the overall outlook for this disorder is poor.<sup>11</sup> When treated with regimens used for diffuse large B-cell lymphoma, complete remissions are seen in less than half the patients, and almost all patients eventually relapse. Whether or not early bone marrow transplantation will increase the likelihood of cure in young patients is a point for study.

Lymphoblastic lymphoma and Burkitt's lymphoma are rare types of aggressive non-Hodgkin's lymphoma that can present with a lymphomatous presentation as tumor masses or as acute leukemia. Lymphoblastic lymphomas are generally treated with acute leukemia-like regimens. Burkitt's lymphoma is most usually managed with specific regimens emphasizing very high doses of cyclophosphamide.<sup>12,13</sup>

### References

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Table 6. PARMA Study Results

Group	Event-Free Survival	Overall Survival
DHAP	12%	32%
ABMT	46%	53%
Significance	p = 001	p = 04

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