Chapter 23
Non-Hodgkin Aggressive B-Cell Lymphoma

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Introduction

Advances in biology during the twentieth century have led us to a better understanding of the nature of lymphomas. We now recognize that what was called "lymphosarcoma" 100 years ago is not a sarcoma, but a complex group of malignancies of lymphoid cells that arise at various stages of cell differentiation. Our immune system includes lymphoid cells and the lymphatic network. Lymphomas thus are cancers of our immune system that arise as a result of unique genetic events that lead to various subtypes of lymphomas that can manifest with very different clinical behaviors and outcomes.

Historically, the lymphomas have been stratified into two broad categories: non-Hodgkin lymphomas (NHLs) and Hodgkin lymphomas (HLs). The NHLs were differentiated from HLs at the turn of the twentieth century with recognition of the unique cells (Reed–Sternberg cells) that characterize the latter. Over the past few decades, medical advances and research have led to enhanced diagnostic capabilities and treatments for patients with NHLs, as well as antitumor drug therapies and combination chemotherapies that have been responsible for significant and steady improvements in survival for these patients. In this chapter, we will review the salient clinical innovations made at MD Anderson Cancer Center that contributed to these advances.

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Epidemiology and Patient Demographics

Lymphomas are cancers that present most commonly in adults. There is a moderate predominance of males over females in the incidence of NHL, about 1.5:1 in most studies, which has persisted for many years. In the USA, there is a higher incidence among Caucasians than among other racial subgroups. The overall incidence of NHL is increasing steadily, although the underlying cause for this trend is not clear. Significant increases in incidence occurred between 1970 and 1995, some of which may have been attributable to the emergence of HIV/AIDS-related lymphomas. These increases in NHL incidence have abated since the late 1990s, yet the overall lymphoma incidence continues to climb. Thus, NHL remains a significant and growing cause of morbidity and mortality. The American Cancer Society estimated that 65,540 new cases of NHL would be diagnosed in 2010 and that 20,210 people would die of this disease [1]. About 55–60% of NHL cases are categorized as "aggressive" lymphomas, and 85–90% of these are of B-cell origin [2].

Advances in Diagnosis and Classification of Lymphomas

Knowledge about the histology, genetics, and behavior of NHL variants has arisen in the past few decades, as have attempts to classify them. Both of these facts make analysis and discussion of NHL necessarily complex. Once thought to be a single disease, we now know that NHL is a heterogeneous group of malignancies with multiple known subtypes. Although the World Health Organization (WHO) classification system currently recognizes more than 30 distinct subtypes of NHL [3], attempts to classify the subtypes of this disease have been ongoing since the 1940s. In the 1950s and 1960s, Rappaport and Rye categorized the few known subtypes pathologically by cell morphology and lymph node histology. The classification systems of the 1970s recognized new variants, which correlated with a new understanding of the immune system and recognition of cell origins (Lukes and Collins classification). In the 1980s, a classification system was developed that attempted to acknowledge patterns with clinical, rather than just pathologic, relevance. Three broad categories emerged from this system: low-, intermediate-, and high-grade disease. These became the backbone of the 1982 International Working Formulation (IWF), an NCI initiative that attempted to synthesize classifications from various systems [4].

Since the advent of the IWF, there have been more refinements in how we view lymphomas, due in large measure to a growing knowledge of the complexity of the lymphatic system and of the ways in which cell lineages within B and T cells interact to maintain immunity. Furthermore, it became evident that unique molecular and genetic events correlate with categories of lymphoma. These newly appreciated complexities led to increasingly sophisticated (and complex) classifications, most notably the REAL and WHO classification systems, which acknowledged

Table 23.1 Ann Arbor staging system

Stage	Definition
I	Involvement of a single lymph node region or a single extranodal organ or site
II	Involvement of two or more lymph node regions on the same side of the diaphragm, or localized involvement of an extranodal organ or site and one or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm with or without localized involvement of an extranodal organ or site or spleen or both
IV	Diffuse or disseminated involvement of one or more distant extranodal organs with or without involvement of lymph nodes

Definition of B symptoms: Fever >38 °C, drenching night sweats, and/or weight loss >10% of body weight in the preceding 6 months

immunophenotypic, genetic, molecular, and some clinical characteristics [3, 5]. Dr. Sattva Neelapu summarizes the classification systems in Tables 22.1 and 22.2 of Chap. 22, "Non-Hodgkin Indolent B-Cell Lymphoma."

"Aggressive" NHL Defined

Clinically, a useful way to look at NHL includes its natural history:

- *Indolent:* Indolent lymphomas are slow-growing and are usually not imminently life-threatening; their clinical course may be stable and not require immediate treatment. Paradoxically, these are less amenable to cure than are more aggressive variants. The indolent lymphomas are discussed by Dr. Sattva Neelapu in Chap. 22.
- *Aggressive:* Aggressive lymphomas require treatment within a short period after presentation; if the illness is not treated, the clinical course will progress and will be fatal. A significant proportion of NHL cases can be cured, but survival outcome can be influenced by a number of critical biological and clinical factors [2]. The first clinical characteristic known to be of significance was the stage of the disease [6] (Table 23.1). A later model of risk, called the International Prognostic Index, included the lymphoma stage and added four other factors: age; whether multiple extranodal sites of involvement are present; the overall performance status of the individual; and the lactic dehydrogenase serum level [7] (Table 23.2).

MD Anderson Cancer Center Experience

Because of the evolving nature of classification in lymphoma diagnostic categories across a span of 60 years, it is difficult to absolutely stratify identical categories as aggressive. However, we mapped the historically described correlation of clinical behavior to categories of lymphomas in each of the major periods of pathologic

Table 23.2 Survival % at 5 years by International Prognostic Index (IPI) score

Each of the following risk factors constitutes 1 IPI score point	
Age	>60 years
Serum LDH	> Upper normal limit
Performance status	≥2 (by ECOG criteria)
Extranodal disease	>1 site
Ann Arbor stage	III or IV
Survival % at 5 years by IPI score	
IPI score	**5-year survival (%)**
0–1	73
2	51
3	43
4–5	26

ECOG Eastern Cooperative Oncology Group, *LDH* lactic dehydrogenase

classification. Thus, we included the large cell histologies from the older classification systems. From the IWF, we included all of the subtypes in the intermediate- and high-grade categories, but excluded lymphoblastic lymphoma. From the REAL and WHO classification systems, we included the mantle cell subtypes, all large B-cell subtypes, follicular lymphoma grade 3B, Burkitt-like lymphomas, and high-grade B-cell lymphomas otherwise not classified. Because the most common subtype of aggressive lymphoma (diffuse large cell) is predominantly of B-cell origin and the next most common subtype (mantle cell) is always of B-cell origin, we described our analysis as most relevant to aggressive B-cell disorders. However, we acknowledge that before 1980 there was no consistent classification that addressed the immunohistologic identity of the T-cell or NK-cell lymphomas. Retrospectively, however, we know that the percentage of lymphomas that are not of B-cell origin constitute at most 15% of the total and so were included among the other lymphomas in the decades before standardized immunohistology.

Our data set was derived from a population of 10,003 patients who presented with the above-noted histologies at our institution between 1944 and 2004 (Table 23.3). Adding to the complexity of any analysis of NHL outcome is the fact that a certain percentage of patients present with a history of prior malignancy. For this discussion, we excluded patients who had received previous treatment, those treated elsewhere, and those who had additional primary cancers, resulting in 3,271 patients who were treated at MD Anderson for these lymphomas. Of these, most had diffuse large cell lymphoma (73%), followed by mantle cell lymphoma (13%) (consisting of the histology categories of mantle cell + diffuse small and intermediate cleaved cell), follicular large cell (6%) and high-grade lymphomas (high-grade B-cell lymphomas + diffuse small non-cleaved cell (6%), and other histologies (2%) (Table 23.4).

Table 23.3 Patients with aggressive non-Hodgkin lymphoma presenting at MD Anderson Cancer Center between 1944 and 2004

Patient characteristics	No. of patients
Total number	10,003
No previous treatment	5,151
Definitive MD Anderson treatment	3,969
No other primaries except superficial skin cancers	3,271

Table 23.4 Aggressive lymphoma histologies in Tumor Registry, 1944–2004

Histologies	Number (%)
Diffuse large cell	2,380 (73)
Follicular large cell/follicular grade 3b	194 (6)
Mantle cell/diffuse small and intermediate cleaved cell	425 (13)
High-grade B-cell/diffuse small non-cleaved cell	190 (6)
Diffuse mixed cell lymphoma/other histologies	82 (2)
Total	*3,271 (100)*

Survival Trends of Patients with Aggressive Lymphomas

The increase in overall survival for patients with aggressive lymphomas is notable not only for its continuous positive trend over the 60-year time frame (Fig. 23.1), but also for the dramatic survival improvements seen during certain time frames, in particular between 1965 and 1985 and again between 1995 and 2004 (Table 23.5). The overall trend can be attributed to the continuous advances and refinements in the use of chemotherapy and the development of new therapeutic agents. The more dramatic jumps can be attributed to a number of significant breakthroughs and milestones, including the advent of combination chemotherapies, bone marrow stem cell transplantation, second-line combinations for salvage in relapsed disease, and specific cell surface antigens that have led to targeted treatments. The application and innovation of these advances at MD Anderson Cancer Center are discussed in the following sections.

Advances in Frontline Chemotherapy

Combination Chemotherapy

The idea of using a chemotherapeutic approach in the treatment of cancers has a long history. William Osler's 1894 *Textbook of Medicine* referred to Fowler's Solution (an arsenic compound) for the treatment of lymphosarcomas. But it was not until after World War II that research gave us nitrogen mustard, a compound that

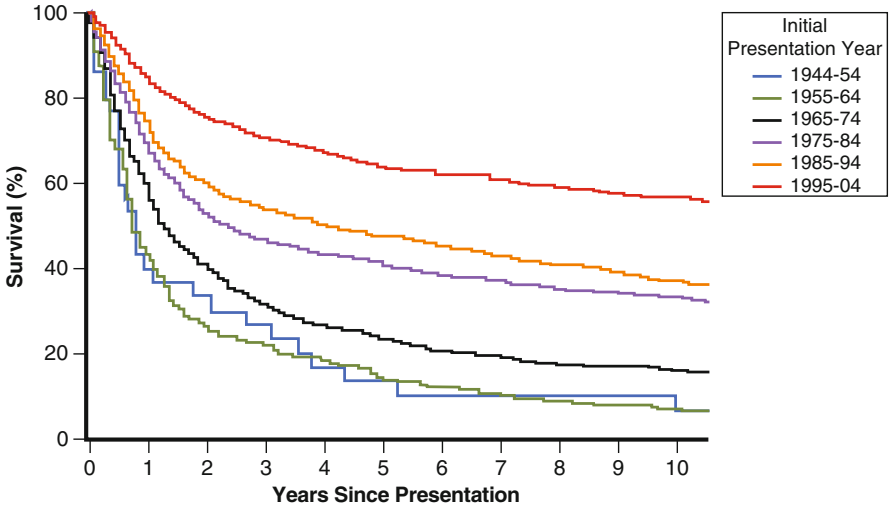

Fig. 23.1 Overall survival rates for patients with non-Hodgkin aggressive B-cell lymphoma who were treated at MD Anderson between 1944 and 2004 ($P < 0.0001$, log-rank test for trend). The salient developments that influenced survival outcomes of aggressive lymphomas were as follows: 1960s–1970s: Introduction of doxorubicin, etoposide, and other novel chemotherapy agents into frontline combination regimens for advanced-stage disease, and combined-modality therapy (chemoradiation) for early-stage disease. 1980s: Development of second-line salvage regimens for recurrent disease, introduction of autologous stem cell transplants, and biologic identification of subtypes of lymphomas. 1990s: Hematopoietic growth factor support agents that allowed more intense dose chemotherapy in frontline treatment as well as autologous stem cell transplantation as consolidation for salvage treatments. Late 1990s–2000: Rituximab, a targeted immunotherapeutic agent against B cells, was combined with chemotherapy.

Table 23.5 Percent survival by decade

	Percent survival	
Decade	5 years	10 years
1944–1954	13.3	6.7
1955–1964	13.9	6.7
1965–1974	23.4	16.2
1975–1984	41.0	33.0
1985–1994	47.9	37.0
1995–2004	63.8	57.5

was proven effective in Hodgkin lymphoma. Other effective agents soon followed, including other alkylating agents and vinca alkaloids, antitumor antibiotics such as doxorubicin, epipodophyllotoxins such as etoposide, and multiple regimens for combination therapies. Thus, cancer chemotherapy was established in the latter part of the twentieth century, and the specialty of medical oncology was born.

The first chemotherapy combination to prove effective in treating aggressive lymphomas was CHOP (cyclophosphamide, 750 mg/m^2 intravenously [IV] on day 1; hydroxydaunomycin [doxorubicin], 50 mg/m^2 IV on day 1; vincristine [Oncovin], 1.4 mg/m^2 IV on day 1, not to exceed 2 mg total; and prednisone, 100 mg by mouth daily on days 1–5). Clinical studies by Jeffrey A. Gottlieb at MD Anderson and his colleagues were a significant milestone in the introduction of the then novel drug doxorubicin in the treatment of aggressive lymphomas [8, 9]. The initial phase II protocol of the CHOP regimen designed by Dr. Gottlieb resulted in complete remissions of large cell lymphomas, even in advanced Ann Arbor stage III–IV disease (Table 23.1). From that point forward, the design of all future frontline regimens for aggressive lymphomas included doxorubicin. A subsequent trial by the Southwest Oncology Group (SWOG) confirmed a significant long-term survival benefit for this regimen in the treatment of advanced-stage large cell lymphomas. Thus, the CHOP regimen became the international gold standard in the frontline treatment of large cell lymphomas and has remained so until the early part of the present century, despite the interim development of numerous other regimens, none of which proved superior to CHOP in randomized trials [10].

Synergy of Immunotherapy and Chemotherapy

The next major advance in the frontline treatment of large cell lymphoma did not arrive until more than 20 years after the design of CHOP and was due to more specific knowledge of the biologic characteristics of B-cell lymphomas. The recognition of unique cell surface complex molecules on B cells, such as the CD-20 antigen, led to the development of agents that could specifically target those molecular antigens with the intent of activating the body's own immune response against the lymphoma. The most notable agent in this category of treatments has been rituximab, a monoclonal antibody that targets the CD-20 B-cell surface antigen complex. It was initially tested in indolent NHL, in a large clinical multi-institutional phase II trial led by Peter McLaughlin, a colleague at our institution. This trial led to FDA approval of this immunotherapeutic agent in 1997 for use in indolent relapsed B-cell lymphomas, but it was promptly integrated into therapy for aggressive B-cell lymphomas in multiple trials. A randomized trial was conducted in Europe by the French cooperative GELA group, in which the addition of rituximab to CHOP (RCHOP) was compared with CHOP. The results demonstrated a statistically superior response and overall survival for the patients with large B-cell lymphoma who were treated with RCHOP compared with those who received CHOP [11]. These results were evident across low- and high-risk International Prognostic Index categories (Table 23.2) and have been confirmed by other trials. Thus, RCHOP has become the new international standard for the treatment of large B-cell lymphomas.

Radiation Therapy and Its Role in Large Cell Lymphoma

Before the development of effective chemotherapy regimens, early-stage (localized) aggressive NHL (stages I and II) was historically treated with radiation therapy (RT) alone. Although many studies were undertaken to improve on results by adjusting radiation dosages and field coverage, it was the addition of combination chemotherapy to RT regimens that improved outcome most dramatically. CHOP was integrated with RT in collaborative trials at MD Anderson for limited-stage large cell lymphoma, with favorable and sustained long-term remissions [12].

To date, four randomized trials have been conducted in early-stage aggressive NHL, all before anti-CD-20 rituximab therapy was incorporated into CHOP chemotherapy. The most well known in the USA is the SWOG study in which eight cycles of CHOP were compared with three cycles of CHOP followed by involved-field RT (40–55 Gy) in limited-stage (I/II) diffuse large B-cell lymphoma. The combined-modality arm, versus the CHOP-only arm, achieved superior overall survival [13]. Thus, combined-modality therapy (chemotherapy plus radiation) remains the standard approach for localized-stage large cell lymphoma. A retrospective case-controlled analysis conducted in patients treated with RCHOP plus RT at our institution, compared with control patients who received RCHOP but not RT, suggested that RT combined with RCHOP is beneficial [14]. However, randomized trials comparing RCHOP with and without RT should be conducted to address the two most pressing unresolved issues—the benefit of RT when patients are in complete remission after RCHOP chemotherapy, and the optimal number of chemotherapy cycles when RCHOP is combined with RT.

Intensified-Dose Chemotherapy

Another significant development in the treatment of aggressive lymphomas at MD Anderson Cancer Center was seen when intensified-dose chemotherapy regimens were used to treat adult lymphomas. The increased sophistication of pathologic diagnoses that included immunohistochemical analyses, as well as cytogenetic and molecular genetic studies, led to the recognition of a new entity called mantle cell lymphoma in the 1980s. Mantle cell lymphoma is aggressive, and survival rates have been poor with CHOP treatment. An intense-dose combination regimen known as HyperCVAD had been developed by Sharon Murphy and her colleagues at another institution to treat childhood lymphoblastic leukemias. Hagop Kantarjian and colleagues at our institution pioneered the application of the HyperCVAD regimen to treat adult lymphoblastic and Burkitt lymphomas, with results in adults as favorable as those in children [15]. Using the same HyperCVAD regimen as front-line treatment, followed by consolidation with autologous stem cell transplantation, Issa Khouri, Jorge Romaguera, and their colleagues at our institution demonstrated long-term survival benefits in young patients with mantle cell lymphomas who received this intensive treatment approach [16].

With the reported benefit of combining rituximab with CHOP in large cell lymphomas, the HyperCVAD regimen for mantle cell lymphoma was similarly combined with rituximab (RHCVAD), showing similar synergy of chemotherapy and immunotherapy as that observed in large cell lymphoma. The treatment of mantle cell lymphoma continues to evolve today, with the development and approval of a new class of targeted drugs, the proteosome inhibitors, to treat this disease. The most well studied of the drugs in this class is bortezomib, which in combination with RHCVAD is currently being evaluated in frontline trials.

Advances in Salvage Treatment

Alternative Combinations After CHOP

A series of lymphoma trials in the 1980s and 1990s at MD Anderson Cancer Center, led by Fernando Cabanillas, William Velasquez, and colleagues, confirmed that using different categories of drugs in second-line therapy after CHOP could lead to response and salvage in recurrent large cell lymphoma. The concept behind these trials was that although the malignant cells might have become resistant to the chemotherapy drugs in the frontline regimen, second-line exposure to drugs of different classes could lead to non-cross-resistant tumor response. Before the development of salvage regimens, a recurrence of large cell lymphoma or a refractory (not responsive) case of large cell lymphoma treated with CHOP meant certain death. Today, there are a number of salvage (second-line) regimens in use that were derived from the seminal work of these pioneers, including cytarabine and cisplatinum combinations (DHAP, ESHAP, and ASHAP) and ifosfamide and etoposide combinations (IE, MINE, and MIME) [17, 18]. These trials were very critical to the further development of the present-day treatment strategies for recurrent/refractory disease (such as the regimen ICE).

Autologous Stem Cell Transplant Consolidation

In the 1980s, another critical new treatment concept was born with the introduction of autologous stem cell transplantation to overcome the limitations of high-dose chemotherapy. The use of autologous stem cell transplants in lymphomas was introduced at MD Anderson by Karel Dicke and Gary Spitzer. Phase II studies showed that this method (high-dose chemotherapy consolidation with stem cell rescue post-salvage treatment for relapse) could lead to durable remissions and survival in patients with relapsed large cell lymphoma [19]. These seminal phase II studies were followed by a large international collaborative randomized trial, the PARMA study. The results of this trial demonstrated that patients with large cell lymphoma

who responded to second-line chemotherapy had improved survival when this response was consolidated with autologous stem cell transplantation [20]. Thus, autologous stem cell transplant consolidation after response to second-line salvage became the standard of care for aggressive lymphomas.

Advances in Supportive Care

Improvements in supportive care have contributed in a significant way to cancer therapy outcomes by reducing the adverse effects of treatment. The supportive management of neutropenia with hematopoietic growth factors to stimulate recovery of neutrophils is critical to the treatment of lymphomas, in particular for patients receiving more intense chemotherapy regimens as well as salvage regimens and stem cell transplants. These agents decrease early mortality due to infections in patients undergoing chemotherapy [21]. Also important is the consultative expertise of infectious disease specialists who focus on cancer-related infectious complications and the appropriate antibiotic management for febrile neutropenia, since infections are the most significant life-threatening complication for patients undergoing autologous stem cell transplantation and receiving intensified-dose chemotherapy regimens. The patients' quality of life is significantly affected as well by appropriate medical management of pain, nausea, and fatigue. Multidisciplinary care, along with specialized nursing care and access to other allied health professionals who specialize in the care of cancer patients, is in no small part responsible for improved outcomes for patients receiving care in comprehensive cancer centers and is particularly important when patients are undergoing intensive therapies.

Future Directions

Continued improvements—durable remissions and increased survival—for aggressive lymphomas are likely to come from building on the trends that have brought us thus far:

- Continued advances in understanding the molecular and genetic profiles of lymphomas
- Development of additional novel targeted therapies that potentiate or replace traditional chemotherapies and thereby reduce the toxicity of treatment
- Continued development of second-line therapies for refractory or relapsed disease

The challenge remains to refine our knowledge about the unique molecular mechanisms that distinguish the various subtypes of NHL and to develop targeted treatments that are more suited to the illness and better tolerated by patients. The

latter would expand the number of patients eligible to receive definitive therapy and hopefully minimize downstream toxicities. The continued refinement in our knowledge of the biologic and molecular genetic nature of NHL is also the key, we hope, to one day being able to prevent them.

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