My Treatment Approach to Patients With Diffuse Large B-Cell Lymphoma

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Abstract

My favored treatment approach for patients with diffuse large B-cell lymphoma continues to evolve. Diffuse large B-cell lymphoma can now be cured in more than 50% of patients. This is a result of improved definitions of the disease, improved diagnostic capabilities, better staging and restaging techniques, a useful prognostic index to guide therapeutic decisions, and the development of increasingly effective therapies. Positron emission tomographic scans have improved the accuracy of both staging and restaging. Findings on a positron emission tomographic scan at the end of therapy are the best predictors of a good treatment outcome. Numerous subtypes of diffuse large B-cell lymphoma have been identified that require specific treatment approaches. For example, plasmablastic lymphoma typically lacks CD20 and does not benefit from treatment with rituximab. Diffuse large B-cell lymphoma originating in specific extranodal sites such as the central nervous system, testes, and skin presents special problems and requires specific treatment approaches. A subgroup of diffuse large B-cell lymphoma with a very high proliferative rate seems to have a poor outcome when treated with CHOP-R and does better with regimens used for patients with Burkitt lymphoma. New insights into the biology of these disorders are likely to further change treatment approaches. Recognition that diffuse large B-cell lymphoma is not one disease, but a variety of clinicopathologic syndromes provides the opportunity to further improve our ability to benefit patients.

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Diffuse large B-cell lymphoma is the most common non-Hodgkin lymphoma, making up approximately 30% to 35% of all cases. Our ability to care for patients with diffuse large B-cell lymphoma has improved dramatically during the past 40 years. This improvement came as a result of clear definitions of the disease, better diagnostic capabilities, improved staging and restaging techniques, the development of a useful prognostic index, and the development of increasingly effective therapies. Since the first reports that patients with what today we call diffuse large B-cell lymphoma could be cured with chemotherapy,^{1,2} recognition of the key role of anthracyclines and, subsequently, rituximab in the cure of these patients has brought us to a place where more than half can be cured.

In 2007 I had the opportunity to describe my treatment approach for patients with diffuse large B-cell lymphoma in an article published in the journal *Blood*.³ Although many of the principles of care elucidated in that article still apply, new insights into the biology of this disease (perhaps better stated as “diseases”) and the results of clinical trials have led to changes in some aspects of the way I care for these patients. I first review those principles of care that I believe have not, and in some cases should not be, substantively changed. The rest of this article focuses on the way new knowledge that has become available in the past 5 years has altered the way I care for these patients.

WHAT HAS NOT CHANGED?

Approach to the Patient

Diffuse large B-cell lymphoma is a potentially fatal but also a potentially curable illness. Patients need and deserve an interested, caring, patient physician who will effectively communicate, listen, and respond to their concerns. Patients with this disease require much more than a physician who simply orders the right tests and administers an appropriate therapeutic regimen.

Diagnosis

The most important step in the treatment of patients with this lymphoma continues to be an accurate diagnosis. Management should always be based on an adequate (ie, usually excisional) biopsy reviewed by an expert hematopathologist. In some circumstances, tissue from a cutting-needle biopsy will be adequate for diagnosis and the safest approach. I am unwilling to treat patients when the diagnosis is based entirely on a fine-needle aspirate specimen.

Predicting Treatment Outcome

No better prognostic system than the International Prognostic Index (IPI)⁴ has been developed (Table 1). Because it can be remembered easily (as long as you can misspell the word “aples”) and retains prognostic significance with new treatment approaches, it continues to be a useful aid in treatment planning.

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TABLE 1. Predicting Treatment Outcome in Diffuse Large B-Cell Lymphoma^a

IPI adverse risk factors (APLES)		
Age >60 y		
Performance status ≤ECOG grade 2		
Lactate dehydrogenase >maximum normal		
Extranodal sites ≥2		
Stage III or IV		
Outcome by risk group with or without rituximab		
Adverse IPI risk factors	4-year event-free survival (%) ^b	
	Without rituximab	With rituximab
1	68	80
2	48	62
3	39	50
4-5	20	47

^aECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index.

^bEstimates from Ziepert et al.⁶

However, since the introduction of rituximab the survival in all IPI groupings has improved.^{5,6}

The "Standard" Treatment Regimen

For most patients, CHOP-R-21 remains an excellent treatment approach. (See Glossary of Chemotherapy Regimens for explanation of abbreviations used in this article.) Although CHOP-14 originally appeared to have a better outcome than CHOP-21 in patients older than 60 years,⁷ the results of studies combining rituximab with CHOP administered at either 14- or 21-day intervals have shown no advantage over CHOP-R-14 and have suggested a higher frequency of toxicity.^{8,9} Randomized trials have found the French ACVBP-R regimen to be superior to CHOP-R in younger patients, although toxicity precludes its use in older patients.^{10,11} However, one of the components of this regimen, vindicine, is not available in the United States. Phase 2 trials with the infusional regimen EPOCH-R have reported excellent results, and a trial comparing this approach with CHOP-R is in progress in the United States. Whether or not these more complicated regimens provide benefit to all patients with diffuse large B-cell lymphoma, I believe that certain patients should receive these regimens today (ie, as discussed later in the article). For most patients with disseminated disease, I use CHOP-R-21. I do restaging after 4 cycles and if necessary again at 6 cycles, with a goal of treating 2 cycles after documenting remission. For those with localized lymphoma, I administer

either 6 cycles of CHOP-R-21 (4 if no disease remains after surgery) or 4 cycles and involved-field radiotherapy.

Central Nervous System Prophylaxis

One of the most serious complications for a patient with diffuse large B-cell lymphoma who presents with disease outside the central nervous system (CNS) is the development of CNS metastasis. This usually involves the cerebrospinal fluid and meninges, but solid parenchymal brain metastasis can also occur. The latter seems more frequent with lymphoma originating in certain extranodal sites such as the testes.¹²⁻¹⁴ Although some patients who develop CNS metastasis after apparently successful treatment for systemic diffuse large B-cell lymphoma can be rescued with treatment including an autologous hematopoietic stem cell transplant,^{15,16} this complication is usually fatal. For that reason, patients thought to be at high risk for developing CNS involvement typically receive prophylactic therapy to attempt to reduce its frequency. The most common treatment used to prevent meningeal metastasis has been intrathecal methotrexate plus or minus cytarabine with or without additional intravenous high-dose methotrexate. Two large series of patients treated using this approach found an incidence of CNS relapse between 1% and 2%.^{17,18} However, in 2 large series of patients in which CNS prophylaxis was not routinely given, the incidence of CNS relapse was 2.2% and 2.8%.^{19,20} In a recent report the incidence of CNS relapse in patients who received rituximab with CHOP was significantly lower than that in patients who received CHOP alone (6.4% vs 9.7%), and the results were even more striking for patients who achieved a complete remission (5.8% vs 2.2%),²¹ suggesting that intravenous rituximab might reduce the incidence. We have seen similar results at the University of Nebraska Medical Center, with a CNS relapse rate of 3.6% with CHOP and 2.2% with CHOP-R ($P=.05$).

It is clear that most patients with diffuse large B-cell lymphoma are at a low risk of CNS metastasis. For patients whose CNS metastasis is destined to appear coincident with systemic relapse, the value of prophylaxis might be marginal. Factors reported to be associated with CNS relapse include specific sites of involvement (ie, nasopharyngeal, epidural, testicular, and other extranodal sites such as breast, adrenal gland, bone, and bone marrow), high serum lactate dehydrogenase, low serum albumin, age younger than 60 years, and more extensive disease.²²

It has been, and remains, my practice to recommend CNS prophylaxis using intrathecal methotrexate given with each cycle of CHOP-R to patients who present with epidural involvement, nasopharyngeal involvement, testicular involvement, and in-

involvement of the bone marrow by large cell lymphoma (ie, in most cases, bone marrow involvement in diffuse large B-cell lymphoma is by small cleaved cells^{23,24}). I consider, and might recommend, prophylactic therapy in patients with unusual extranodal sites such as adrenal gland, kidney, and bone. It appears that some patients destined to develop meningeal metastasis from diffuse large B-cell lymphoma have cells present in the spinal fluid at diagnosis that can be detected by flow cytometry.^{25,26} Although I have not routinely performed spinal taps on patients with newly diagnosed diffuse large B-cell lymphoma, doing so might be one way to identify patients who should have aggressive "prophylactic" therapy.

The Use of Radiotherapy

Controversy continues regarding the place of radiotherapy in the management of patients with diffuse large B-cell lymphoma who have sites of bulky disease at presentation. The definition of bulky disease has varied from 5 to 10 cm in different reports. Some physicians believe that a patient who achieves a complete remission with a rituximab-containing regimen, particularly if defined by negative results on a positron emission tomographic (PET) scan, does not require consolidative radiotherapy to sites of bulky disease. However, a recent report from MD Anderson Cancer Center found that radiotherapy after CHOP-R chemotherapy improved 5-year progression-free survival (90% vs 75%) and overall survival (91% vs 83%) in patients with all stages of disease.²⁷

Long follow-up of patients from the MabThera International Trial suggested there still might be a place for radiotherapy after treatment including rituximab for those with bulky disease. This trial compared 6 cycles of a CHOP-like regimen with the same regimen plus rituximab²⁸ in younger patients with diffuse large B-cell lymphoma that had a good prognosis. Patients received radiotherapy to sites of initially bulky disease after the completion of chemotherapy. Radiotherapy seemed to eliminate the anticipated negative prognostic impact of bulky disease.²⁹

I still offer radiotherapy to most patients with sites of bulky disease (ie, ≥ 10 cm) regardless of the initial stage of disease. An equivocal PET scan result at the completion of treatment would make me more likely to administer the radiotherapy.³⁰

The Place of Transplantation

Autologous hematopoietic stem cell transplant remains the best treatment for patients with chemotherapy-sensitive relapse. The place of autologous hematopoietic stem cell transplant after relapse fol-

lowing a rituximab-containing regimen has been questioned.³¹ However, a recent report from the United Kingdom suggested that patients who remain chemotherapy sensitive after relapse are still best treated with an autotransplant.³² The authors found a 5-year event-free survival of 51% in historical patients who received only CHOP and 72% in patients who received a transplant after relapse who were initially treated with CHOP-R. Either RICE or DHAP appears to be a reasonable regimen to use for cytoreduction before transplant.³³ I usually use RICE.

Whether an autotransplant should be offered to any patient who presents with very high-risk disease as an adjuvant after a remission induced with a rituximab-containing chemotherapy regimen remains problematic. However, a recent report from the US intergroup study found a better failure-free survival (75% vs 41%) and overall survival (82% vs 64%) for high-IPI patients who received transplants in complete remission or partial remission after 6 cycles of CHOP-R vs those who received 2 more cycles of CHOP-R.³⁴ There may still be some patients who would be appropriate for transplant in first remission.

Allogeneic transplant has limited utility in the treatment of patients with diffuse large B-cell lymphoma. A recent report from the Center for International Blood and Marrow Transplant Research showed a significantly higher 1-year treatment-related mortality (41% vs 12%), a similar frequency of relapse after transplant, and a lower 5-year overall survival (22% vs 49%) with allogeneic transplant than with autologous transplant.³⁵ However, it is clear that a few patients can undergo allogeneic hematopoietic stem cell transplant, usually with a reduced-intensity preparative regimen, and achieve prolonged disease-free survival after autotransplant failure.^{36,37} I rarely recommend allogeneic transplant to a patient with diffuse large B-cell lymphoma. I always favor autologous transplant as part of the treatment for an initial relapse. I have occasionally recommended allogeneic transplant to a young, fit patient who has failed autologous transplant and has an HLA-matched sibling donor.

Surveillance Imaging in Remission

There is still no proof that surveillance imaging benefits patients with diffuse large B-cell lymphoma being followed up in remission. In fact, there is some evidence that it can be detrimental,³⁸ and it adds to the cost of care. My personal approach continues to be to see patients at 2-month intervals in the first year of follow-up, 3-month intervals for the second year, 4-month intervals for the third year, 6-month intervals for 2 years, and then once a year indefinitely. I believe seeing patients more frequently

shortly after treatment allows the physician to help them during a time of particular anxiety and that extending the time between visits in a regular way helps them feel confident that things are going well. Each visit consists of a thorough history and physical examination and routine laboratory studies. Imaging studies and appropriate biopsies are performed only when a new finding raises a question of relapse. I have a few patients whose friends or neighbors receive routine images and wonder if they might benefit from them. Most patients are satisfied by a discussion about the potential benefits and risks of routine images in remission. However, if the patient wants the images, I am willing to do them.

The Diagnosis of Relapse

Perhaps the most important issue in caring for patients with diffuse large B-cell lymphoma in remission is never to initiate treatment for relapse in the absence of a biopsy that proves relapse. My colleagues and I have kept track of the “surprise” diagnoses in patients with “obvious” relapse whom we have seen over the years.³ These include other malignancies, other lymphomas, infections (ie, fungal or mycobacterial), and sarcoidosis. In the past few years we have had patients in whom we considered starting therapy for what seemed obvious relapse who, on biopsy, had histoplasmosis, coccidiomycosis, and sarcoidosis. Patients who achieve a complete remission and might be cured should *never* be treated for relapse without proving recurrence of their lymphoma.

WHAT HAS CHANGED?

Increasing Importance of PET Scans

When fluorodeoxyglucose PET (hereafter referred to as PET) scans were first introduced into the care of patients with lymphoma, it was quickly apparent that they had great potential to influence care. However, as a quote attributed to Bear Bryant, the great Alabama football coach, regarding the great potential of a young football player goes, “Potential is what they ain’t done yet.” We have now reached the point that PET scans have fulfilled much of their early potential in the care of patients with diffuse large B-cell lymphoma, and the possibility exists that interim PET scanning could further change the management of patients with this disease. PET scans should always be done with a combined PET and computed tomography (CT) scanner to maximize accuracy.

Diffuse large B-cell lymphoma is one of the most consistently PET-avid lymphomas.³⁹ The standard uptake value (SUV) is typically high, with most lymphomas having an SUV_{max} greater than 10 and

many having an SUV_{max} greater than 20. PET scans improve the accuracy of staging, with as many as 20% to 40% of patients having their stage altered after the performance of a PET scan.⁴⁰⁻⁴³ Perhaps the most important contribution of PET scans to current management of patients with diffuse large B-cell lymphoma is in documenting complete remission. It has become clear that PET scans are more accurate than CT scans in proving complete remission and that a negative PET scan result has the greatest impact in predicting progression-free and overall survival.⁴⁴⁻⁴⁸ In fact, current restaging guidelines specify that a negative PET scan result is a key factor in documenting complete remission—something that is particularly useful in patients who have a residual mass on CT scan.⁴⁹

I try to have a PET scan performed as part of staging in all patients with diffuse large B-cell lymphoma. Achieving a negative PET scan result is the criterion I use for documenting complete remission. However, a borderline-positive PET scan at the completion of therapy does not necessarily mean persistent disease. In patients with localized disease, radiotherapy is often administered in this setting. In patients with disseminated disease, either performing a biopsy or waiting for 1 to 2 months and repeating the scan to see if results have normalized is a reasonable approach.

One of the new topics in applying PET scans to the treatment of patients with diffuse large B-cell lymphoma is the use of early, or interim, scans to predict treatment outcome after only 1 to 3 cycles of treatment. Some studies,^{50,51} but not all,^{52,53} have found a dramatic impact on eventual treatment outcome. The group from Vancouver has reported the use of PET scans after 3 cycles of therapy with CHOP-R for patients with localized diffuse large B-cell lymphoma.⁵⁴ Patients with a positive scan result received radiotherapy, while those with a negative scan result received one more cycle of CHOP-R. With use of this approach, only 1 of 49 patients who were PET-negative subsequently relapsed (2-year progression-free survival, 97%), while 3 of 16 patients who had a positive PET scan result subsequently relapsed (2-year progression-free survival, 82%).

At the present time I do not use PET scans after 2 or 3 cycles of treatment to direct therapy. However, it is possible that this will become the standard treatment approach in the future.

Although surveillance PET scans in patients with diffuse large B-cell lymphoma in remission are not specific and should not be routinely performed, in patients in whom relapse is suspected, PET scans can be extremely useful in identifying the best site to biopsy. Unfortunately, many insurance companies will not authorize a PET scan in this setting.

Patients With Heart Disease

Patients with congestive heart failure who develop diffuse large B-cell lymphoma present a difficult problem. Doxorubicin, the most active traditional chemotherapeutic agent in diffuse large B-cell lymphoma, is associated with a significant risk of worsening of the heart failure, and most physicians believe it would be contraindicated. A number of approaches have been proposed to treat these patients. These include deleting doxorubicin from CHOP-R, substituting mitoxantrone for doxorubicin, substituting liposome-encapsulated doxorubicin,⁵⁵ substituting etoposide for doxorubicin, using bendamustine-R,⁵⁶ and substituting procarbazine for doxorubicin.²

The approach that I have adopted was recently reported by the Vancouver group.⁵⁷ They described 81 patients who either had cardiac contraindications to the use of doxorubicin or received a previous anthracycline for a different disorder. These patients were matched 2:1 to previously treated patients without contraindications to doxorubicin and who received CHOP-R. The patients who could not take doxorubicin instead received etoposide, 50 mg/m² on day 1 and 100 mg/m² on day 2 and day 3. The 5-year freedom-from-progression rate was 62% in the CHOP-R patients and 57% in the patients who received etoposide. The overall survival rate favored CHOP-R (64% vs 49%).⁵⁷ I believe this is a reasonable approach to patients in whom doxorubicin is contraindicated.

Recognition of Distinct Subtypes That Might or Do Require Special Treatment Approaches

The 2008 version of the World Health Organization (WHO) classification of lymphoid malignancies recognizes numerous subtypes of diffuse large B-cell lymphoma.⁵⁸ As shown in Table 2, these include morphologically, immunologically, genetically, and clinically defined variants in addition to a few miscellaneous categories. In addition, there are tumors that exist on the interface between diffuse large B-cell lymphoma and Burkitt lymphoma and between mediastinal large B-cell lymphoma and Hodgkin lymphoma, other rare clinical presentations such as leukemic diffuse large B-cell lymphoma, double-hit diffuse large B-cell lymphomas, and those with a very high proliferative rate—often with an *MYC* translocation. As we become more sophisticated at subdividing patients with diffuse large B-cell lymphoma, it would seem reasonable to suspect that biologically unique entities might be identified that would require special treatment approaches. It is increasingly clear that this is, in fact, the case. I will deal here with those groups in which I believe modification of the therapeutic approach is appropriate (Table 3).

TABLE 2. Diffuse Large B-Cell Lymphoma in the New World Health Organization Classification

• Centroblastic	• Primary CNS	• EBV-positive in elderly
• Immunoblastic	• Primary cutaneous, leg type	• With chronic inflammation
• Anaplastic	• Mediastinal	• Lymphomatoid granulomatosis
• Plasmablastic	• Intravascular	• In HHV-8 associated Castleman disease
• T-cell rich	• Primary effusion	
• ALK-positive		
• CD5-positive		
• GCB		
• Non-GCB		

ALK = anaplastic lymphoma kinase; CNS = central nervous system; EBV = Epstein-Barr virus; GCB = germinal center B-cell; HHV-8 = human herpesvirus 8.

Morphologic Variants Requiring Treatment Modification

Plasmablastic lymphoma is a diffuse proliferation of large cells that resemble immunoblasts but have the immunophenotype of plasma cells.⁵⁹ It can occur de novo or as a transformation of other plasma cell neoplasms, including multiple myeloma. This lymphoma was originally thought to be seen predominantly in individuals positive for the human immunodeficiency virus (HIV), with presentation involving the oral cavity. However, it is now clear that this lymphoma can also occur in patients who are not infected with HIV and have other, although predominantly extranodal, presenting sites. In one series of plasmablastic lymphoma in HIV-negative patients, 89% presented with extranodal involvement, although only 21% had involvement of the oral cavity.⁶⁰ The overwhelming majority of patients with plasmablastic lymphoma will have tumors that are CD20-negative. Therapy with rituximab will not benefit these patients, and it should not be used unless the patient has one of the rare plasmablastic lymphomas that is CD20-positive. Treatment with regimens such as CHOP has typically yielded complete response rates of less than 50% and a median survival of 1 year or less. It is possible that combining drugs such as bortezomib with CHOP, or performing autotransplants in remission for those patients who achieve a complete remission, might improve the treatment outcome.

Lymphomatoid granulomatosis is an Epstein-Barr virus–positive B-cell lymphoproliferative disorder that usually arises in patients with no history of immunodeficiency. The condition is a progressive immune disorder that involves the lung and other organs such as the CNS, skin, liver, and kidney. The disorder is an angiocentric and angi destructive process that is known to evolve into diffuse large B-cell lymphoma in some cases.⁶¹ Lymphomatoid granulomatosis itself is graded on a scale of 1 to 3 based on the extent of Epstein-Barr virus–positive B cells and the level of necrosis. Grade 3 lymphomatoid

TABLE 3. Diffuse Large B-Cell Lymphoma Variants and Related Disorders Requiring Special Treatment Approaches

	Special treatment approaches
Morphological variants	
Plasmablastic	Usually CD20-negative, so rituximab is not useful
DLBCL arising from lymphomatoid granulomatosis	Sometimes relapses as low-grade lymphomatoid granulomatosis and can be treated with interferon or rituximab
Specific sites of involvement	
Testes	Frequent CNS metastasis and recurrence in the opposite testicle necessitate CNS prophylaxis and scrotal irradiation
CNS	Does not benefit from CHOP-R and requires high-dose intravenous methotrexate-based regimen
Skin	Must distinguish between cutaneous DLBCL, leg type, which requires systemic treatment such as CHOP-R, and other tumors (termed cutaneous follicle center cell lymphoma) that need only local treatment
Highly proliferative variants	
Lymphoma with features intermediate between DLBCL and Burkitt lymphoma	Have a high failure rate with CHOP-R and are best treated with Burkitt regimens (eg, EPOCH-R, CODOX-M/IVAC)
Double-hit lymphoma (MYC and BCL-2)	
MYC-positive	
Other subtype	
Mediastinal gray zone lymphoma	The best treatment is uncertain. The most common treatment is CHOP-R followed by radiotherapy

CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma.

granulomatosis is often monoclonal and often evolves into, and behaves like, diffuse large B-cell lymphoma. Patients with low-grade lymphomatoid granulomatosis can be effectively managed with interferon or rituximab, and some patients can have durable responses.⁶² However, patients with high-grade lesions and those that have transformed to diffuse large B-cell lymphoma should be treated with regimens known to be effective in diffuse large B-cell lymphoma, such as CHOP-R. Investigators at the US National Cancer Institute have utilized EPOCH-R for patients with high-grade or transformed lymphomatoid granulomatosis and for patients with

low-grade disease in whom interferon therapy failed and have found a high overall survival. My approach is to treat patients whose disease is transforming to diffuse large B-cell lymphoma with CHOP-R, and I have treated patients with lower-grade disease with rituximab. It is important to realize that some patients who present with diffuse large B-cell lymphoma arising in lymphomatoid granulomatosis and achieve a remission will relapse with lower-grade lymphomatoid granulomatosis. I have one such patient who underwent salvage treatment with rituximab and has had a durable remission.

Specific Anatomic Sites That Require Treatment Modification.

Diffuse large B-cell lymphoma presenting as a brain tumor, with or without meningeal or ocular involvement, is being seen increasingly in HIV-negative patients. Therapy with CHOP-R or with primary radiotherapy has a poor outcome, with a median survival of less than 1 year. It is now clear that treatment regimens that include high-dose methotrexate plus or minus high-dose cytarabine plus or minus consolidative radiotherapy can achieve long-term, disease-free survival in 30% to 50% of patients, with the best results in younger patients.⁶³ Our team tries to avoid radiotherapy in the primary treatment regimen to reduce the risk of the development of dementia in long-term survivors. This is a particularly serious problem in patients who are treated after 60 years of age. However, in patients in whom primary chemotherapy regimens fail, radiotherapy provides an important palliative option.⁶⁴

Diffuse large B-cell lymphoma is the most common testicular tumor in men older than 60 years. It has been known for some time that this lymphoma follows an atypical clinical course. Late relapse (ie, after >5 years of remission) is seen frequently. Patients often have recurrent disease in the opposite testicle if they do not receive scrotal radiotherapy, and CNS metastases (ie, sometimes parenchymal masses) occur frequently.⁶⁵ A recent clinical trial conducted by the International Extranodal Lymphoma Study Group treated patients with CHOP-R plus intrathecal methotrexate and scrotal radiotherapy.⁶⁵⁻⁶⁷ The 53 treated patients had a complete response rate of 98%, 5-year progression-free survival of 74%, and 5-year overall survival of 85%. The 5-year risk of recurrence in the contralateral testicle was 0%, and the 5-year risk of CNS relapse was 6%. Of course, these patients remain at risk for late relapse. At the present time I believe this is the best treatment approach for patients with primary testicular lymphoma and the one that I offer to my patients.

Patients with cutaneous B-cell lymphomas who are diagnosed as having diffuse large B-cell lym-

phoma might fit into 1 of 2 categories. Primary cutaneous diffuse large B-cell lymphoma, leg type, typically presents on the lower legs of elderly women.⁶⁸ My experience has been that these tumors pursue an aggressive course and most patients do not achieve a durable remission with regimens such as CHOP-R. I have seen other patients with cutaneous B-cell lymphoma, often presenting on the scalp and often in younger patients, diagnosed as diffuse large B-cell lymphoma. These tumors probably belong in the WHO category primary cutaneous follicle center cell lymphoma.⁶⁹ These patients have a tumor that is best treated with excision or involved-field radiotherapy and do not require systemic therapy. Because the treatment and prognosis vary so widely, it is important to make every effort to distinguish between these 2 entities.

Intravascular and leukemic diffuse large B-cell lymphoma represent 2 other variants. Both are rare presentations of diffuse large B-cell lymphoma. Only the intravascular large B-cell lymphoma has a category in the WHO classification.⁷⁰ Patients with intravascular diffuse large B-cell lymphoma often present diagnostic dilemmas. The tumors grow in association with endothelial cells and can disrupt the function of any involved organ. Patients likely to be seen in the United States often present with CNS or cutaneous manifestations. However, the last patient I saw presented with liver failure. In the absence of a high degree of suspicion, these patients might not be diagnosed until an autopsy. In fact, they are often subjects of clinicopathologic conferences. There is also an Asian variant that typically presents with hepatosplenomegaly, pancytopenia, and hemophagocytic syndrome.

Patients with intravascular diffuse large B-cell lymphoma usually respond to CHOP-R or similar regimens and can have long-term, disease-free survival if they achieve a complete remission.^{71,72} Central nervous system prophylaxis should be considered, and I have offered transplant in complete remission to some patients with this type of diffuse large B-cell lymphoma.

Patients with diffuse large B-cell lymphoma that presents with leukemia (ie, circulating large lymphoma cells) have been thought to have a terrible prognosis. However, a recent series of patients treated at Emory University and the University of Nebraska showed that these patients can achieve a complete remission when treated with rituximab-containing regimens and that these remissions can be durable.⁷³

Highly Proliferative Variants of Diffuse Large B-Cell Lymphoma. A number of subgroups of diffuse large B-cell lymphoma fit under this heading. These include lymphomas at the interface between diffuse large B-cell lymphoma and Burkitt lymphoma,⁷⁴

double-hit lymphoma (for our purposes those with *MYC* rearrangement and *BCL2* rearrangement), diffuse large B-cell lymphomas that overexpress *MYC*, and those that have Ki-67 expression of more than 90% but fit into none of the other subgroups. There is considerable overlap among these groups. For example, approximately 25% to 75% of tumors identified as being at the interface between diffuse large B-cell lymphoma and Burkitt lymphoma are double-hit lymphomas.^{58,75} It is unclear how many of the reported cases of *MYC*-overexpressing diffuse large B-cell lymphomas might actually have been double-hit lymphomas.

It does appear clear that, when treated with CHOP-R-like regimens, patients with double-hit diffuse large B-cell lymphoma have a very poor prognosis, with reported survival ranging from 4 to 25 months and the poorest survival in the largest series.⁷⁵ Patients with these lymphomas typically have poor prognostic features, including advanced stage, elevated lactate dehydrogenase levels, bone marrow positivity, multiple extranodal sites, and CNS involvement.⁷⁶ It is less clear that patients whose diffuse large B-cell lymphomas overexpress *MYC* but are not double-hit lymphomas have a poorer prognosis.^{77,78} Our experience has been that these patients do better than those with double-hit diffuse large B-cell lymphoma, although we generally treat these patients with more intensive regimens. Patients with lymphomas intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma have been reported to have a poorer outcome than those with typical diffuse large B-cell lymphoma, but these patients often have adverse genetic abnormalities, including double hits.⁷⁹ In the experience of others⁸⁰ and ourselves, these patients have done better when regimens usually used for Burkitt lymphoma were employed.

My approach for patients with double-hit lymphomas, tumors that are identified as being at the interface between diffuse large B-cell and Burkitt lymphoma, and tumors that are *MYC*-positive is to use EPOCH-R. The infusional regimen has been shown to have a high cure rate in patients with Burkitt lymphoma⁸¹ and to be at least as effective as CHOP-R in patients with typical diffuse large B-cell lymphoma. I consider performing an autotransplant in first remission, particularly in patients with double-hit lymphomas.

Mediastinal Gray Zone Lymphoma. These lymphomas are at the interface between mediastinal diffuse large B-cell lymphoma and classic Hodgkin lymphoma. They display both morphological and immunophenotypic features typically found in nodular sclerosing Hodgkin lymphoma and mediastinal large B-cell lymphoma.⁵⁸ A recent report suggested

that these lymphomas might be distinct biological entities with a unique gene expression pattern.⁸² Patients with mediastinal gray zone lymphoma have been most commonly treated with regimens active in diffuse large B-cell lymphoma. Interestingly, a recent report from investigators at the National Cancer Institute suggested that patients with mediastinal gray zone lymphoma had a much poorer outcome when treated with EPOCH-R than similar patients with typical mediastinal large B-cell lymphoma.⁸³ My approach to these patients has been to treat them with CHOP-R followed by mediastinal radiotherapy. This treatment can be curative. Whether these patients would be better treated with Hodgkin lymphoma–like regimens, have autotransplants as part of their primary therapy,⁸⁴ or have entirely different treatment approaches needs to be resolved.

Other Subtypes of Diffuse Large B-cell Lymphoma That Might Soon Be Treated Differently. We have known for some time that patients with the activated B-cell (ABC) genetic subtype of diffuse large B-cell lymphoma have a poorer outcome than those with the germinal center B-cell subtype.^{85,86} Tumors with the ABC gene expression pattern consistently overexpress the NF- κ B pathway. A recent report from the National Cancer Institute used the protease inhibitor bortezomib, which inhibits the NF- κ B pathway, in combination with EPOCH-R in patients with relapsed or refractory diffuse large B-cell lymphoma.⁸⁷ The investigators found an improved response rate and overall survival in patients with the ABC subtype. This is leading to prospective trials of bortezomib-containing combination chemotherapy regimens in patients with ABC-type diffuse large B-cell lymphoma.⁸⁸ If the results are positive, this might lead to a change of practice.

A subset of patients with diffuse large B-cell lymphoma overexpresses the protein CD30, which is typically found in anaplastic large-cell lymphoma, albeit at a lower concentration than seen in anaplastic large-cell lymphoma. In addition, a subset of patients with diffuse large B-cell lymphoma overexpresses the protein anaplastic lymphoma kinase (ALK).^{89,90} Brentuximab vedotin has been shown to be highly active in CD30-expressing tumors, and the ALK inhibitor crizotinib has shown to be active in ALK-expressing T-cell lymphomas and lung cancers.^{91,92} If trials are positive, brentuximab vedotin and crizotinib might change practice for patients with CD30-positive and ALK-positive diffuse large B-cell lymphoma.

CONCLUSION

It has become clear that the entity we call diffuse large B-cell lymphoma is made up of a variety of

clinicopathologic syndromes that should not all have identical treatment. As we better understand the biological explanation for these differences (eg, site of involvement, proliferative rate), we might develop more specific and more effective therapies. In the meantime, trying to optimize use of currently available tools (eg, PET scans, chemotherapeutic agents, radiotherapy) through clinical studies will increase our ability to benefit patients with diffuse large B-cell lymphoma. This remains a work in progress, but patients have gained much by the work done to date.

GLOSSARY OF CHEMOTHERAPY REGIMENS

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone

CHOP-R = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

CHOP-R-21 = 21-day cycle of rituximab with standard cyclophosphamide, doxorubicin, vincristine, and prednisone

CHOP-R-14 = 14-day cycle of rituximab with standard cyclophosphamide, doxorubicin, vincristine, and prednisone

EPOCH-R = etoposide, doxorubicin, vincristine (by 96-h infusion) plus cyclophosphamide, prednisone, rituximab

ACVBP-R = rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone—followed by a consolidation regimen and central nervous system prophylaxis

RICE = rituximab, ifosfamide, carboplatin, etoposide

DHAP = dexamethasone, high-dose cytarabine, cisplatin

CODOX-M/IVAC = cyclophosphamide, vincristine, doxorubicin, cytarabine, methotrexate/etoposide, ifosfamide, cytarabine

Potential Competing Interests: The author has been a consultant for Eisai, Seattle Genetics, Spectrum, Genentech, and Ziopharm.

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