Management of Aggressive Lymphoma

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ABSTRACT

Significant progress in the recognition of biologically important subtypes of aggressive lymphoma and a better understanding of its prognostic features have had a major impact on the management of this disease. Although a chemotherapy regimen consisting of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) remains the appropriate treatment for many patients with diffuse large B-cell lymphoma, new treatment modalities and drugs should be considered in many cases. Novel, more specific drugs are likely to have a major impact on the management of non-Hodgkin's lymphoma (NHL) in the next decade.

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INTRODUCTION

The term aggressive non-Hodgkin's lymphoma (NHL) encompasses a heterogeneous group of lymphoid disorders with a rapid growth rate that more or less correspond to intermediate grade lymphomas as defined by the National Cancer Institute's (NCI's) Working Formulation.[1] The recognition of an increasing number of subtypes of NHL that have unique clinical and pathological features renders a general management strategy for aggressive lymphomas impossible.[2] Rather, using the recent World Health Organization (WHO) classification, (Table 1) we will describe the management of the most common entities of aggressive NHL.[3] These include diffuse, large B-cell lymphoma, the closely related grade III follicle center lymphoma, primary mediastinal B-cell lymphoma, anaplastic large cell lymphomas, other peripheral T/natural killer (NK)-cell lymphomas, and mantle cell lymphoma (MCL).

Burkitt's lymphoma and lymphoblastic lymphoma constitute two entities whose clinical behaviors are extremely aggressive (so-called high-grade lymphoma in the Working Formulation). Treatment of these lymphomas is very similar to that used for acute lymphocytic leukemia.[4] Small noncleaved, non-Burkitt's lymphoma is no longer utilized in the WHO classification. Most lymphomas that had been classified previously as such carry a C-myc translocation and are, therefore, likely similar to Burkitt's disease.[5] A large number of unusual types of lymphoma are also included in Table 1.[3] Although many of these entities are exceedingly rare and treatment is standardized poorly, an accurate diagnosis is essential for prognostic purposes.

WORKUP AND STAGING OF AGGRESSIVE NHL

Recommendations for staging workup for NHL are summarized in Table 2; we discuss some salient points. An incisional or excisional biopsy of a lymph node (or of a tumor mass) is usually required. A through-cut biopsy may be an alternative, but fine needle aspiration (FNA) is often insufficient to identify a specific histologic subtype.[6-8] Fresh tissue should always be collected for immunophenotyping and/or molecular analysis. A bone marrow biopsy and aspirate is also part of the routine staging procedure for NHL. Bilateral biopsies are not routinely required.[9] Laboratory tests should include serum lactate dehydrogenase (LDH) and β2-microglobulin, two parameters that have been correlated independently with prognosis. Human immunodeficiency virus (HIV), human T-cell lymphotropic virus (HTLV-1), Epstein-Barr virus (EBV), and hepatitis C virus (HCV) serologies should be obtained when appropriate, as the presence of any of these viruses has important therapeutic implications. We recommend performing HCV testing in all patients with B-cell NHL, especially in areas of high HCV prevalence.[10] We recommend HIV testing of patients in high-risk populations and of patients with high-risk histologies. Gallium scans (single photo emission computed tomography [SPECT] scans) are valuable in detection and follow-up of aggressive NHL.[11-13] Recent reports also suggest a role for positron emission tomography (PET) scanning in monitoring response to therapy.[14-17] PET scanning is probably equivalent or slightly superior to

TALKING POINTS Physicians Pharmacy Formulary Cancer Nurses

The management and prognosis of aggressive non-Hodgkin's lymphoma (NHL) is guided by histologic subtype, extent of disease, and patient-related prognostic features.

The International Prognostic Index (IPI) is a widely used tool to predict the prognosis of patients with aggressive lymphoma treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy or similar regimens.

Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma typically affects adults in their 20s and 30s, and has an excellent prognosis when treated with aggressive combination therapy.

The addition of rituximab to CHOP chemotherapy may improve the outcome of elderly patients with aggressive B-cell NHL.

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gallium scanning and has practical advantages (1 day turnaround). To our knowledge, no formal comparison of PET and gallium studies has occurred. In some cases, the choice of diagnostic tests is guided by the location of the NHL or by specific disease histologies. For example, a magnetic resonance imaging/computed tomography (MRI/CT) scan or bone scan may be needed in lymphoma associated with bone involvement, ensophagogastroduodenoscopy (EGD) and/or upper gastrointestinal (GI) series with small bowel follow-through in patients with primary GI lymphoma. A histologic report of MCL as well as involvement of the Waldeyer's ring in any subtype of NHL warrants a subsequent evaluation of the GI tract. Lumbar puncture should be included in a routine evaluation of NHL known to be associated with high incidence of central nervous system (CNS) involvement. This includes Burkitt's and lymphoblastic NHL, blastic variants of mantle cell NHL, HIV-related NHL, and some subtypes of large cell lymphoma, such as testicular lymphoma, lymphoma of the craniofacial area, and lymphoma in patients with very high International Prognostic Index (IPI) scores.[22]

TABLE 1. CLASSIFICATION SCHEMA FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA (BASED ON REAL/WHO CLASSIFICATION OF LYMPHOPROLIFERATIVE DISEASES)

B-CELL NEOPLASMS

Aggressive/Intermediate Risk

1. Prolymphocytic leukemia
2. Mantle cell lymphoma*
3. Follicle center cell lymphoma: grades III (large cell)*
4. Diffuse large B-cell lymphoma*
5. Primary mediastinal (thymic) large B-cell lymphoma*
6. Lymphomatoid granulomatosis (angiocentric pulmonary B-cell lymphoma)
7. Intravascular large B-cell lymphoma
8. Primary effusion lymphoma

Very Aggressive Lymphoma

9. Precursor B-cell lymphoblastic leukemia/lymphoma
10. Burkitt's lymphoma/B-cell acute lymphocytic leukemia

T-CELL AND PUTATIVE NK-CELL NEOPLASMS

Aggressive

11. Peripheral T-cell lymphoma, unspecified*
12. Extranodal NK/T cell lymphoma, nasal type
13. Enteropathy type T-cell lymphoma
14. Anaplastic large cell lymphoma*
15. Hepatosplenic T-cell lymphoma
16. Primary cutaneous anaplastic large cell lymphoma

*Disorders discussed in this article.
REAL=Revised European American Lymphoma; WHO=World Health Organization; NK=natural killer cells.

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DIFFUSE LARGE B-CELL LYMPHOMA

Approximately 40% of all cases of lymphoma in the Western world (including 70% of all cases of aggressive lymphoma) are diffuse large B-cell lymphoma.[2] Treatment modalities developed originally for intermediate grade lymphoma apply best to diffuse large B-cell lymphoma. Grade III follicular lymphoma (ie, a follicular lymphoma with >15 large cells per high power field) is also considered an aggressive lymphoma and is treated in the same fashion.[3] Morphologic variants of diffuse large B-cell lymphoma include the centroblastic variant, the T-cell histiocyte-rich variant, the immunoblastic variant, and the anaplastic variant (the latter not to be confused with anaplastic large cell lymphoma of T-cell derivation). Although unique clinical or prognostic significance may in the future be attached to some of these variants, currently, their identification warrants no specific management.[18,19]

The management of diffuse large B-cell lymphoma (DLBCL) depends on the stage of the disease and other prognostic features recognized at diagnosis.[20,21] These may be divided into two groups: patient-related factors such as age or general health and tumor-related factors such as stage, bulkiness, high rate of tumor growth, LDH level, β2-microglobulin level, or the specific sites of extranodal involvement.

The IPI developed for aggressive NHL is the most widely used of a number of prognostic systems that incorporate

TABLE 2. RECOMMENDED WORKUP FOR AGGRESSIVE LYMPHOMA

- History and physical examination
- CT scan of chest/abdomen/pelvis
- Gallium scan with SPECT (or PET scan)
- Bone marrow aspirate and biopsy
- Lymph node biopsy (alternative through-cut biopsy):
  - Immunophenotyping
  - Consider molecular studies
  - Consider cytogenetics
- Laboratory tests:
  - Complete blood count, differential, platelets
  - Comprehensive metabolic panel
  - Serum LDH, β-2 microglobulin
  - Consider serum and urine protein electrophoresis
  - Consider HIV, EBV, HCV, HTLV-1 testing
- Additional tests:
  - Lumbar puncture/brain MRI/CT:
    - IPI > 3
    - Testicular lymphoma
    - Sinus lymphoma
    - Blastic variant of mantle cell lymphoma
  - MRI/bone scan:
    - Suspected bone involvement
  - Endoscopy:
    - Waldeyer's ring involvement
    - Mantle cell lymphoma

CT=computed tomography; SPECT=single photon emission computed tomography; PET=positron emission tomography; LDH=lactate dehydrogenase; HIV=human immunodeficiency virus; EBV=Epstein-Barr virus; HCV=hepatitis C virus; HTLV-1=human T-cell lymphotropic virus; MRI=magnetic resonance imaging; IPI=International Prognostic Index.

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some of these features. Such systems are useful but incomplete surrogates for the biologic heterogeneity of NHL. The IPI recognizes four risk groups among patients treated with modern anthracyclin-based chemotherapy (Table 3).[22] The variant of this model for patients younger than age 60 years is referred to as the Age-Adjusted International Prognostic Index. The IPI is a simple and practical tool in pretreatment assessment of patients with aggressive NHL, although the fact that half of the patients with NHL fall into intermediate prognosis categories limits significantly its utility in the treatment of individual patients. Advances in biologic studies of oncogenes, markers of proliferation and apoptosis, as well as gene expression profiling by oligonucleotide microarray technology may, in the future, allow distinction among homogenous subtypes of NHL, which may enable a uniform clinical management and prognosis. Expression of clusters of genes characteristic for germinal centers has already been associated with a more favorable prognosis in one group of B-cell NHL compared with B-cell NHL, whose gene expression profile was more reminiscent of nongerminal center origin.[23] Most recently, expression of the bcl-6 gene as detected by rt-PCR or by immunohistochemistry was found to be a favorable prognostic factor correlated with overall and disease-free survival.[24]

MANAGEMENT

Approximately 40% of patients with intermediate-grade lymphoma are cured with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy, a combination of an anthracyclin, an alkylating agent, a vinca alkaloid, and a steroid.[25,26] Randomized trials completed in the early 1990s failed to reveal a clear advantage of more complex second and third generation chemotherapy regimens over CHOP and, thus, confirmed this relatively simple regimen as the first-line treatment for aggressive NHL.[27-30] Although CHOP chemotherapy continues to be the most appropriate management for many patients, treatment recommendation should be individualized based on risk features and disease localization.[31]

Management of Patients With Localized Nodal or Extranodal Disease

For patients with stage I or low-bulk stage II disease, a brief course of chemotherapy (ie, three cycles of CHOP) followed by involved field radiation is considered optimal management. A Southwest Oncology Group (SWOG) study randomized such patients to three cycles of CHOP plus radiation versus six to eight cycles of CHOP. Progression-free survival (77% versus 64%, P=0.03) and survival (82% versus 72%, P=0.02) were significantly better in patients receiving combined modality treatment.[32] An Eastern Cooperative Oncology Group (ECOG) study randomized patients with slightly more advanced disease (ie, bulky stage I and all stage II disease) who achieved complete remission after eight cycles of CHOP with 30 Gy involved field radiation versus observation. In this study, there was a significant benefit in 6-year disease-free survival for radiation therapy consolidation (73% versus 58%, P=0.03) and a marginal benefit in overall survival (70% versus 84%, P=0.06).[33] Based on these results, it is commonly recommended that patients with bulky stage I disease or stage II disease receive adjuvant radiation after maximal response has been achieved with CHOP chemotherapy. The same recommendation applies to localized extranodal DLBCL, such as large cell lymphoma of the leg or of the stomach.[34,35] Testicular DLBCL is the most common cause of an isolated testicular mass in older males and has some unique clinical features. It is associated with a high rate of CNS involvement and dissemination, therefore, all patients with testicular lymphoma should receive a diagnostic lumbar puncture. CNS prophylaxis, in addition to systemic chemotherapy and involved field radiation, is commonly recommended.[36] In localized testicular lymphoma, irradiation should involve the entire testicular bed to prevent relapse in the opposite site.

Management of Patients With Unfavorable Prognostic Features

The standard of care among patients with noncontiguous stage II, stage III, or stage IV disease consists of six to eight cycles of CHOP chemotherapy. Although such treatment is appropriate for patients with favorable prognostic features

TABLE 3. INTERNATIONAL PROGNOSTIC INDEX FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA[22]

Risk Group	Number of Adverse Risk Factors	Predicted 5-year Survival for Patients < Age 60 Years	Predicted 5-year Survival for Patients of All Ages
1	0–1	85%	73%
2	2	69%	51%
3	3	46%	43%
4	4-5	32%	26%

Note: The risk factors in International Prognostic Index: age (> or <60 years), LDH level (low or elevated), performance status (0–1 vs 2–3), Ann Arbor stage (III vs IV), and extranodal sites (0–1 vs >1). Age Adjusted International Prognostic Index (patients <60 years): LDH (lower or elevated), performance status (0–1 vs 2–3), and stage (I-II vs III–IV).

LDH=lactate dehydrogenase.

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(such as a low IPI score or presence of bcl-6 expression), patients with unfavorable prognostic features should be recommended to participate in investigational treatments. For younger patients with unfavorable prognostic features, dose intensification with autologous bone marrow or stem-cell transplantation has been explored. For elderly patients, the CHOP-rituximab combination has generated considerable interest.

Dose-Intensification in Younger Patients With Adverse Prognostic Features

Dose-intensification with autologous bone-marrow or stem-cell transplantation has been tested in at least six large randomized studies (Table 5). In a small study from the Netherlands, patients with partial remission resulting from CHOP chemotherapy were randomized to high-dose chemotherapy or further CHOP chemotherapy, without any advantage to the transplant arm.[37] In a French multicenter study, patients in complete remission after induction therapy were randomized. An advantage for transplantation was demonstrated in the subgroup of patients who had high IPI scores.[38-40] In an Italian study restricted to a subgroup of patients with bulky DLBCL but without bone marrow involvement, an advantage for transplantation was shown.[41] By contrast, a recent European Organization for Research and Treatment of Cancer (EORTC) report failed to show an advantage for consolidation with autologous transplantation in patients with low or low-intermediate IPI scores.[42] Two other European studies failed to show an advantage to transplantation after an abbreviated induction course.[43,44] The contradictory results are due, in part, to differences in patient eligibility, in transplant methodology, and in the timing of transplantation. Patients with favorable prognoses (ie, low IPI scores) have good outcomes with conventional chemotherapy and are unlikely to benefit from autologous transplantation.[38,42] Autologous transplantation after shortened induction regimens and for patients in partial remission seem not to be of benefit.[37,43,44] Finally, patients with multiple adverse prognostic features have a poor tolerance and response to stem cell-based dose intensification.[41] On the other hand, it is likely that autologous stem cell transplantation used as consolidation of first complete remission improves the outcomes of younger patients with NHL and of some adverse prognostic features, such as bulky disease, by approximately 10–20%.[40] Dose-intensification continues to be investigated in an ongoing intergroup randomized study as well as in an ongoing randomized study at M. D. Anderson Cancer Center.[41,45]

Other Investigational Approaches

A number of Phase II studies of novel therapeutic approaches to the treatment of patients with unfavorable prognostic features have been reported. Vose et al[46] reported a study of CHOP + rituximab (see below) that resulted in durable responses in 15 out of 16 patients with IPI scores >2. The NCI reported on their experience with the EPOCH regimen, a variant of the CHOP regimen that includes etoposide (see Table 4). EPOCH combines two unique features, namely the use of infusional chemotherapy that is hypothesized to fundamentally alter cytotoxicity and the use of a dose-escalation scheme based on nadir granulocyte counts. This regimen also resulted in an 80% durable remission rate and is currently undergoing phase II testing by the Cancer and Leukemia Group B (CALGB).[47]

Treatment of Elderly Patients With Extensive Disease

Treatment of older patients (usually defined as those over the age of 65) constitutes a particular challenge. Their tolerance to CHOP chemotherapy is reduced, and the rate of durable remissions is lower compared to younger patients. On the other hand, attenuated dose regimens were found definitely inferior to CHOP in a number of randomized trials.[48-51]

The relatively poor outcome with CHOP chemotherapy justified the study of CHOP-rituximab as an up-front regimens for elderly patients. Rituximab, a monoclonal, humanized anti-CD20 antibody, has only limited activity in diffuse large cell lymphoma (DLCL), with an overall response rate of 30%, mostly of brief duration.[52] Recently, a European multicenter randomized study that compared CHOP with CHOP-rituximab reported a higher complete remission rate, disease-free survival, and overall survival from the use of a combination of CHOP and rituximab in elderly patients with newly diagnosed aggressive B-cell lymphoma.[53] Follow-up was still extremely limited at a median of 6 months. A US intergroup trial evaluated a similar approach in elderly patients and has completed accrual recently; no results have been reported as of yet. The final results of the European and American trials will establish the role of the CHOP-rituximab regimen for elderly patients with aggressive lymphoma.

Management of Patients With Recurrent Disease

Patients with primary refractory disease or relapsed aggressive NHL may be treated with non-cross–resistant chemotherapy regimens containing drugs such as cisplatin, etoposide, cytarabine, or ifosfamide (Table 4). Complete remission rates with DHAP or ESHAP (see Table 4 for regimen contents) range from 20% to 35%; remissions are usually short, and few, if any, cures are obtained.[54,55] High-dose ifosfamide-based regimens have also been explored. They produce an impressive response rate, but their impact on long-term outcome is comparable with that of more commonly used conventional-dose salvage regimens.[56,57]

Consolidation with high-dose chemotherapy and stem cell transplantation (SCT) is the treatment of choice for patients with relapsed or refractory lymphoma that responded to salvage chemotherapy. The role of stem cell transplantation was established by the randomized PARMA trial.[58] In this study, patients responding to salvage (DHAP) were randomized to continue with conventional chemotherapy or to receive high-dose chemotherapy with SCT. Disease-free survival (46% versus 12%) and overall

TABLE 4. THE MOST COMMONLY USED CHEMOTHERAPY REGIMENS FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA

Chemotherapy Regimen	Dose	Route and Frequency
CHOP:		
Cyclophosphamide	750 mg/m²	IV, on day 1
Doxorubicin	50 mg/m²	IV, on day 1
Vincristine	1.4 mg/m² (max 2 mg)	IV, on day 1
Prednisone	100 mg	PO, on days 1–5
		Repeat cycle every 21 days
DHAP:		
Dexamethasone	10 mg	PO, q6h, days 1–4
Cytarabine	2 g/m²	IV, q12h X 2 doses, on day 2
Cisplatin	100 mg/m²	IV, 24-hour continuous infusion on day 1
		Repeat cycle every 21–28 days
ESHAP:		
Etoposide	60 mg/m²	IV, on days 1–4
Cisplatin	25 mg/m²	IV, on days 1–4
Cytarabine	2 g/m²	IV, q12h X 2 doses, on day 2, immediately following completion of etoposide and cisplatin
Methylprednisolone	500 mg	IV, on days 1–4
		Repeat cycle every 21–28 days
IMVP-16:		
Ifosfamide	5 g/m²	IV, 24-hour continuous infusion on day 1
Mesna	800 mg/m²	IV, bolus prior to ifosfamide
	4 g/m²	IV, 24-hour continuous infusion with ifosfamide
	2.4 g/m²	IV, 12-hour continuous infusion after ifosfamide on day 2
Methotrexate	30 mg/m²	IV, on days 3 and 10
Etoposide	100 mg/m²	IV, on days 1–3
		Repeat cycle every 21–28 days
MINE:		
Mesna	1,330 mg/m²	IV, on days 1–3 with ifosfamide PO 4 hour and 8 hours after each ifosfamide dose
Ifosfamide	1,330 mg/m²	IV, on days 1–3
Mitoxantrone	8 mg/m²	IV, day 1
Etoposide	65 mg/m²	IV, days 1–3
		Repeat cycle every 28 days
MINE/ESHAP: (See above for the exact description of MINE and ESHAP)		*Repeat MINE every 21 days for six courses, then start ESHAP. If complete response is achieved with MINE, consolidate with three courses of ESHAP. If there is only a partial MINE response, then administer six courses of ESHAP*
EPOCH:		
Etoposide	50 mg/m²	IV, 24-hour continuous infusion on days 1–4
Vincristine	0.4 mg/m²	IV, 24-hour continuous infusion on days 1–4
Doxorubicin	10 mg/m²	IV, 24-hour continuous infusion on days 1–4
Cyclophosphamide	750 mg/m²	IV, on day 6
Prednisone	60 mg/m²	PO, daily on days 1–6
		Repeat cycle every 21 days. Dosing is based on nadir WBC
ICE:		
Etoposide	100 mg/ m²	IV, on days 1–3
Carboplatin	AUC 5 (max 800 mg)	IV, on day 2
Ifosphamide	5,000 mg/ m²	IV, 24-hour continuous infusion on day 2
Mesna	5,000 mg/ m²	IV, 24-hour continuous infusion on day 2
Rituximab/CHOP:		
Rituximab	375 mg/m²	IV, day 1
CHOP regimen (see above)		Begin on day 3
		Repeat every 21 days
Ifosfamide/etoposide:		
Ifosfamide	3.3 gr/m²	IV, daily X 3 days
Etoposide	150 mg/m²	IV, q12h X 6 days
Mesna	10 gr/m²	IV, over 3 days

WBC=white blood cell count; AUC=area under the curve.

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survival (53% versus 32% at 5 years) rates for patients treated with SCT were significantly better. Among patients with recurrent DLBCL, the chemosensitivity of the disease as measured by the response to the salvage treatment is a commonly used predictor for success with SCT.[59] Additionally, duration of first remission and the IPI score at recurrence have been used to predict outcome in this setting.[57,60,61] Patients with high IPI scores and/or a short duration of first remission may be better served by participation in investigational studies. Allogeneic transplantation or variations on autologous transplantation that include post-transplant therapy are some of the new approaches being tested. Several years ago we reported encouraging outcomes with the use of allogeneic transplantation in patients with refractory lymphoma,[62] but in most studies the treatment-related mortality of allogeneic transplantation has adversely affected outcomes and limited its impact.[63] Renewed interest in allogeneic transplantation has been generated by the development of nonmyeloablative and T-cell depleted SCT protocols.[64,65]

PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Primary mediastinal large B-cell lymphoma (PMBL) is a distinct clinicopathologic entity with unique phenotypic and molecular features; it arises from an intrathymic B-cell population.[66] Using classic pathologic criteria, the disease can be difficult to distinguish from other DLBCL, but it has a quite distinctive clinical presentation.[66,67] PMBL is most common in young adults, who present with a large mass in the anterior mediastinum. It occurs slightly more commonly in women. It accounts for approximately 5% of all aggressive lymphomas and for a much higher percentage of young patients. The presenting symptoms are most often attributable to a large mediastinal mass invading the surrounding tissue such as pericardium, lungs, pleura, and chest wall or to superior vena cava syndrome. Bone marrow involvement at the time of diagnosis is rare. The aggressive nature of PMBL requires prompt diagnosis, which should be followed by administration of uninterrupted treatment with a full-dose anthracycline-based regimen. Several investigators advocate the use of regimens more intensive than CHOP, such as MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin).[68-70] Patients with significant residual mass (>20% of original size) or persistent gallium uptake upon completion of conventional chemotherapy have a relatively high risk for recurrence, and we recommend consolidation with SCT for such patients.[66,71,72] Others have recommended consolidative irradiation to the chest for all patients with locally advanced disease.[73] Patients who achieve complete remission should be followed closely. The vast majority of relapses occur within the first 6–12 months following completion of treatment. The success rate of salvage treatment with SCT in relapsed or primary refractory disease is considerable[72,74]; on the other hand, salvage with radiation therapy is ineffective in patients who fail conventional-dose chemotherapy.[66]

ANAPLASTIC LARGE CELL LYMPHOMA

Anaplastic large cell lymphoma (ALCL) is an aggressive lymphoma characterized by anaplastic morphology and the expression of CD30, that is, Ki-1 antigen.[3,75] The term ALCL encompasses two biologically different disorders that are distinguished by the expression of the ALK protein (anaplastic lymphoma kinase). ALK expression can be detected by immunohistochemistry and together with CD30 expression is essential for diagnosis. ALK-positive ALCL is a T-cell disorder as demonstrated by the presence of T-cell receptor gene rearrangement. Translocation (2;5) is typical and leads to expression of the ALK protein. A number of alternative translocations occur that lead to a similar disease entity with expression of ALK. A proportion of cases lack expression of T-cell markers and are, therefore, called null-cell ALCL, although T-cell receptor gene rearrangement can be demonstrated in such patients. Patients with ALK-positive ALCL tend to be young, with a slight male preponderance. They usually present with advanced disease and nodal as well as extranodal (skin, bone, soft tissue, lung, liver) involvement. With aggressive anthracycline-based chemotherapy, long-term survival approaches 70%.[75,76] A subset patients with ALCL lack t(2;5) and are ALK-negative. They are typically somewhat older than the average patient with ALK-positive ALCL. The long-term survival of these patients is less than 20%, strongly suggesting a biologically different nature of ALK-positive versus ALK-negative disease. Primary cutaneous ALCL is yet another distinct entity among anaplastic Ki-positive lymphomas.[75] It occurs de novo or develops in the background of lymphomatoid papuloosis, mycosis fungoides, or Hodgkin's disease. ALCL with B-cell immunophenotype is rare and should be considered a variant of B-cell DLCL.[3] Hodgkin's-like ALCL cases, after careful review, can usually be reclassified as tumor cell-rich classic Hodgkin's lymphoma or nodal ALCL, ALK positive or ALK negative.[3]

PERIPHERAL T/NK-CELL LYMPHOMA

The detailed analyses of all subtypes of peripheral T-cell DLCL recognized by REAL/WHO classification is beyond the scope of this review. With the exception of well-defined entities such as anaplastic large cell lymphoma, mycosis fungoides, or HTLV-1 related lymphoma/leukemia for which diagnostic criteria and management approaches are relatively defined, much remains to be characterized about the peripheral T/NK-cell lymphomas.[3] Most types of peripheral T-cell lymphomas are treated like B-cell DLCL. The IPI score has prognostic importance similar to B-cell DLCL, but nonanaplastic T-cell phenotype confers an unfavorable prognosis.[2,77-83] Chances for long-term, disease-free survival based on treatment with anthracycline-based chemotherapy are poor, especially in subtypes such as hepatosplenic T-cell lymphoma or enteropathy-like lymphoma. A recent report suggests that prognosis may be improved by consolidation with autologous transplantation.[76] There is also considerable interest in the development of new agents

for the treatment of peripheral T-cell lymphoma. Considerable activity has been observed with retinoids,[84] 2CDA,[85] and with the investigational drug 506U78(Ara-G).[86] Campath 1H, a monoclonal anti-CD52 that was approved for treatment of refractory chronic lymphocytic leukemia (CLL), also has considerable activity in T-prolymphocytic leukemia (T-PLL) and may be investigated as part of a stem-cell-purging strategy.[87]

MANTLE CELL LYMPHOMA

Mantle cell lymphoma (MCL) is an aggressive B-cell lymphoma with unique clinical, morphologic, and biological characteristics.[88] The usual age at diagnosis ranges between age 50 and 70 years. MCL is often widespread at diagnosis; bone marrow involvement and peripheral blood involvement are common. Involvement of the spleen, liver, or Waldeyer's ring or diffuse involvement of the GI system are common. Sometimes GI involvement presents as multiple lymphomatous polyposis. Diagnosis relies on morphology (the lymphoma cells have a pattern of differentiation that is "intermediate" between that of CLL and follicular lymphomas), immunophenotyping (CD5, CD19 phenotype), immunohistochemistry (overexpression of cyclin D1), cytogenetics (t11;14 in up to 30% of patients), or molecular analysis (bcl1 gene rearrangement).[3,88] The prognosis of MCL is worse than and the duration of response to therapy is shorter than those achieved in other types of diffuse lymphoma.[89] Blastoid and pleomorphic variants, as well as those with mutations of the p53 gene, have even worse prognosis and may be at high risk for CNS recurrence. One unusual subset, mantle zone lymphoma (ie, those cases in which the disease proliferates in the mantle zone of the follicle) has an indolent behavior and a good response to conventional chemotherapy. The optimal treatment for MCL is not well established. Intensive chemotherapy, autologous or allogeneic transplantation, and/or interferon maintenance may all play a treatment role.

Intensive chemotherapy regimens such as the hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) regimen may increase response rates and duration of response. Equally impressive rates for complete remission and disease-free survival have been reported recently as a result of up-front high-dose chemotherapy followed by SCT; however, the follow-up in these studies was rather limited as numbers were small.[90,94] Earlier trials of autologous transplantation in MCL showed

TABLE 5. STUDIES OF AUTOLOGOUS TRANSPLANTATION VS CONVENTIONAL CHEMOTHERAPY AS INITIAL TREATMENT FOR AGGRESSIVE NHL

Author	Inclusion Criteria	Randomization	Number Enrolled	Chemotherapy	Number Randomized	DFS (95% CI)	Survival	Comments
Haioun et al, 2000[40]	Age: 16–55 WF: IGL or HGL	CR after induction with intensive chemotherapy	916	LNH84 vs LNH84 + BMT	541	62% vs 54%	69% vs 67%	Significant benefit in IPI 3–4
Verdonck et al, 1995[37]	Age 15–60 WF: IGL & IBL Stages II, III, IV	PR after CHOP X 3	286	CHOP X 8 vs CHOP X 3 + CYTBI	69	72% vs 60%	85% vs 56%	No significant benefit
Gianni et al, 1997[41]	Age: 17–60 B-cell DLC & IBL, bulky (>10 cm) without BM involvement	Upon initiation of chemotherapy	98	MACOP-B vs intensive sequential + SCT	98	49% vs 84%	55% vs 81%	Significant benefit in DFS
Kluin-Nelemans, 2001[42]	Age: 15–60 DLC & IBL	PR after CHVmP/BV X 3	311	5 cycles CHVmP/BV vs 3 cycles CHVmP/BV + ABMT	194	56% vs 61%	77% vs 68%	No significant benefit
Reyes et al, 1997[43]	Age: <60 DLC & IBL, AaIPI: 2–3	Upon initiation of chemotherapy	370	Conventional chemotherapy vs intensive induction + SCT	370	54% vs 41%	63% vs 47%	Disadvantage for intensive induction + SCT
Kaiser et al, 1999[43]	Age: <60 DLC & IBL, LDH elevated	Upon initiation of chemotherapy	312	CHOEP X 5 vs CHOEP X 3 + SCT	312	54% vs 64%	68% vs 64%	No significant benefit

AaIPI=Age-adjusted International Prognostic Index; ABMT=autologous bone marrow transplantation; BM=bone marrow; BMT=bone marrow transplantation; CHOEP=cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; CHOP= cyclophosphamide, doxorubicin, vincristine, prednisone; CHVmP/BV=cyclophosphamide, doxorubicin, vindesine, prednisone, bleomycin; CI=confidence interval; CR=complete remission; CYTBI=cyclophosphamide and total body irradiation; DFS=disease-free survival; DLC=diffuse large-cell lymphoma; HGL=high grade lymphoma; IBL=immunoblastic lymphoma; IGL=intermediate grade lymphoma; IPI=International Prognostic Index; LDH=lactate dehydrogenase; LNH84=intensive doxorubicin-based induction regimen; MACOP-B=methotrexate, doxorubicin, cyclophosphamide, vincristine, predinisone-bleomycin; PR=partial remission; SCT=stem cell transplantation; WF=working forumulation.

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very high recurrence rates.[91] Therefore, the inclusion of SCT in first-line treatment of MCL remains controversial.

Rituximab was reported to be quite efficacious in MCL and is being added frequently to first-line regimens such as hyper-CVAD or CHOP.[92] As a single agent it can produce a response rate of 20–38%, with some patients achieving complete remission. Rituxan is especially effective in eliminating lymphoma cells from the blood and bone marrow, and it has also been used as an "in vivo purging" agent with encouraging early results.[93] **OS**

REFERENCES

1. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. *Cancer.* 1982;49:2112-2135.
2. The Non-Hodgkin's Lymphoma Pathologic Classification Project. A clinical evaluation of the international lymphoma study group classification of non-Hodgkin's lymphoma. *Blood.* 1997;89:3909-3918.
3. Jaffe ES, Harris NL, Stein H, Vardiman JW. World Health Organization classification of tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Vol.1. Lyon, France: IARC Press; 2001:1-351. World Health Organization classification of Tumours. Kleihues, P. and Sobin, L. H. Ref Type: Serial (Book and Monograph).
4. van Besien K, Cabanillas F. Clinical manifestations, staging and treatment of non-Hodgkin's lymphoma. In: Hoffman R, Benz EJ, Shattil SJ, et al, eds. *Hematology, Basic Principles and Practice.* 3rd ed. New York: Churchill Livingstone; 2000:1293-1339.
5. Braziel RM, Arber DA, Slovak ML, et al. The Burkitt-like lymphomas: a Southwest Oncology Group study delineating phenotypic, genotypic, and clinical features. *Blood.* 2001;97:3713-3720.
6. Pinkus GS. Needle biopsy in malignant lymphoma. *J Clin Oncol.* 1996;14:2415-2416.
7. Pappa VI, Hussain HK, Reznek RH, et al. Role of image-guided core-needle biopsy in the management of patients with lymphoma. *J Clin Oncol.* 1996;14:2427-2430.
8. Ben-Yehuda D, Polliack A, Okon E, et al. Image-guided core-needle biopsy in malignant lymphoma: experience with 100 patients that suggests the technique is reliable. *J Clin Oncol.* 1996;14:2431-2434.
9. Cheson B, Horning S, Coiffier B, Shipp MA, Fisher RA, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphoma. *J Clin Oncol.* 1999;17:1244-1253.
10. Zuckerman E, Zuckerman T, Levine AM, et al. Hepatitis C virus infection in patients with B-cell non-Hodgkin's lymphoma. *Ann Intern Med.* 1997;127:423-428.
11. Kaplan WD, Jochelson MS, Herman TS, et al. Gallium-67 imaging: a predictor of residual tumor viability and clinical outcome in patients with diffuse large-cell lymphoma. *J Clin Oncol.* 1990;8:1966-1970.
12. Vose JM, Bierman PJ, Anderson JR, et al. Single-photon emission computed tomography gallium imaging versus computed tomography: predictive value in patients undergoing high-dose chemotherapy and autologous stem-cell transplantation for non-Hodgkin's lymphoma. *J Clin Oncol.* 1996;14:2473-2479.
13 Janicek M, Kaplan W, Neuberg D, Canellos GP, Shulman LN, Shipp MA. Early restaging gallium scans predict outcome in poor-prognosis patients with aggressive non-Hodgkin's lymphoma treated with high-dose CHOP chemotherapy. *J Clin Oncol.* 1997;15:1631-1637.
14. Jerusalem G, Beguin Y, Fassotte MF, et al. Persistent tumor 18F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma. *Haematol.* 2000;85:613-618.
15. Jerusalem G, Beguin Y, Fassotte MF, et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for post-treatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. *Blood.* 1999;94:429-433.
16. Romer W, Hanauske AR, Ziegler S, et al. Positron emission tomography in non-Hodgkin's lymphoma: assessment of chemotherapy with fluorodeoxyglucose. *Blood.* 1998;91:4464-4471.
17. Spaepen K, Stroobants S, Dupont P, et al. Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([18F]FDG) after first-line chemotherapy in non- Hodgkin's lymphoma: is [18F]FDG-PET a valid alternative to conventional diagnostic methods? *J Clin Oncol.* 2001;19:414-419.
18. Engelhard M, Brittinger G, Huhn D, et al. Subclassification of diffuse large B-cell lymphomas according to the Kiel classification: distinction of centroblastic and immunoblastic lymphomas is a significant prognostic risk factor. *Blood.* 1997;89:2291-2297.
19. Maes B, Anastasopoulou A, Kluin-Nelemans JC, et al. Among diffuse large B-cell lymphomas, T-cell-rich/histiocyte-rich BCL and CD30+ anaplastic B-cell subtypes exhibit distinct clinical features. *Ann Oncol.* 2001;12:853-858.
20 Coiffier B, Salles G, Bastion Y. Prognostic factors in non-Hodgkin's lymphomas. In: Magrath IV, ed. *The Non-Hodgkin's Lymphomas.* 2nd ed. London: Arnold; 1997:739-768.
21. Shipp MA. Prognostic factors in aggressive non-Hodgkin's lymphoma: who has "high-risk" disease? *Blood.* 1994;83:1165-1173.
22. The International Non-Hodgkin's Lymphoma Prognostic Factors Project: a predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med.* 1993;329:987-994.
23. Alizadeh A, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature.* 2000;403:503-511.
24. Lossos IS, Jones CD, Warnke R, et al. Expression of a single gene, BCL-6, strongly predicts survival in patients with diffuse large B-cell lymphoma. *Blood.* 2001;98:945-951.
25. Gottlieb JA, Gutterman JU, McCredie KB, Rodriguez V, Frei E, III. Chemotherapy of malignant lymphoma with adriamycin. *Cancer Res.* 1973;33:3024-3028.
26. McKelvey EM, Gottlieb JA, Wilson HE, et al. Hydroxyldaunomycin (adriamycin) combination chemotherapy in malignant lymphoma. *Cancer.* 1976;38:1484-1493.
27. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med.* 1993;328:1002-1006.
28. Gordon LI, Harrington D, Andersen J, et al. Comparison of a second-generation combination chemotherapeutic regimen (m-BACOD) with a standard regimen (CHOP) for advanced diffuse non-Hodgkin's lymphoma. *N Engl J Med.* 1992;327:1342-1349.
29. Sertoli MR, Santini G, Chisesi T, et al. MACOP-B versus ProMACE-MOPP in the treatment of advanced diffuse non-Hodgkin's lymphoma: results of a prospective randomized trial by the non-Hodgkin's Lymphoma Cooperative Study Group. *J Clin Oncol.* 1994;12:1366-1374.
30. Cooper IA, Wolf MM, Robertson TI, et al. Randomized comparison of MACOP-B with CHOP in patients with intermediate-grade non-Hodgkin's lymphoma: the Australian and New Zealand Lymphoma Group. *J Clin Oncol.* 1994;12:769-778.
31. Canellos GP. CHOP may have been part of the beginning but certainly not the end: issues in risk-related therapy of large cell lymphoma. *J Clin Oncol.* 1997;15:1713-1716.
32. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med.* 1998;339:21-26.
33. Glick JH, Kim K, Earle J, O'Connell MJ. An ECOG randomized phase III trial of CHOP vs CHOP + radiotherapy for intermediate grade early stage non-Hodgkin's lymphoma [abstract]. *ASCO Proceedings.* 1995;14:1221.

34. Sarris AH, Braunschweig I, Medeiros LJ, et al. Primary cutaneous non-Hodgkin's lymphoma of Ann Arbor stage I: preferential cutaneous relapses but high cure rate with doxorubicin-based therapy. *J Clin Oncol.* 2001;19:398-405.
35. Koch P, Del Valle F, Berdel WE, et al. Primary gastrointestinal non-Hodgkin's lymphoma, II. combined surgical and conservative or conservative management only in localized gastric lymphoma-results of the prospective German multicenter study GIT NHL 01/92. *J Clin Oncol.* 2001;19:3874-3883.
36. Touroutouglou N, Dimopoulos MA, Younes A et al. Testicular lymphoma: late relapses and poor outcome despite doxorubicin-based therapy. *J Clin Oncol.* 1995;13:1361-1367.
37. Verdonck LF, Van Putten WLJ, Hagenbeek A, et al. Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive non-Hodgkin's lymphoma. *N Engl J Med.* 1995;332:1045-1051.
38. Haioun C, Lepage E, Gisselbrecht C, et al. Comparison of autologous bone marrow transplantation with sequential chemotherapy for intermediate-grade and high-grade non-Hodgkin's lymphoma in first complete remission: a study of 464 patients. *J Clin Oncol.* 1994;12:2543-2551.
39. Haioun C, Lepage E, Gisselbrecht C, et al. Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor-risk aggressive non-Hodgkin's lymphoma: updated results of the prospective study LNH87-2: Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol.* 1997;15:1131-1137.
40. Haioun C, Lepage E, Gisselbrecht C, et al. Survival benefit of high-dose therapy in poor-risk aggressive non- Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol:a Groupe d'Etude des Lymphomes de l'Adulte study. *J Clin Oncol.* 2000;18:3025-3030.
41. Gianni AM, Bregni M, Siena S, et al. High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. *N Engl J Med.* 1997;336:1290-1297.
42. Kluin-Nelemans HC, Zagonel V, Anastasopoulou A, et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. *J Nat Cancer Inst.* 2001;93:22-30.
43. Reyes F, Lepage E, Morel P, et al. Failure of first-line inductive high-dose chemotherapy in poor risk patients with aggressive lymphoma: updated results of the randomized LNH93-3 study. *Blood.* 1997;90(suppl 1):594a. Abstract 2640.
44. Kaiser U, Uebelbacker I, Birkmann J, Havemann K, and German high-grade lymphoma study group. High dose therapy with autologous stem cell transplantation in aggressive NHL: results of a randomized multi-center study. *Blood.* 1999;94:611a. Abstract 2716.
45. Fisher RI. Autologous bone marrow transplantation for aggressive non-Hodgkin's lymphoma: lessons learned and challenges remaining. *J Nat Cancer Inst.* 2001;93:4-5.
46. Vose JM, Link BK, Grossbard M, et al. Phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. *J Clin Oncol.* 2001;2:389-397.
47. Wilson WH, Grossbard M, Alvarez M, et al. Dose-escalating EPOC chemotherapy in previously untreated large cell lymphoma. *Proc Am Assoc Clin Oncol.* 1998;17:17a. Abstract 65.
48. Bastion Y, Blay JY, Divine M, et al. Elderly patients with aggressive non-Hodgkin's lymphoma: disease presentation, response to treatment, and survival: a Groupe d'Etude des Lymphomes de l'Adulte study on 453 patients older than 69 years. *J Clin Oncol.* 1997;15:2945-2953.
49. Sonneveld P, de Ridder M, Van der Lelie H, et al. Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. *J Clin Oncol.* 1995;13:2530-2539.
50. Tirelli U, Errante D, Van Glabbeke M, et al. CHOP is the standard regimen in patients > 70 years of age with intermediate-grade and high-grade non-Hodgkin's lymphoma: results of a randomized study of the European organization for research and treatment of cancer lymphoma cooperative study group. *J Clin Oncol.* 1998;16:27-34.
51. Meyer RM, Browman GP, Samosh ML, et al. Randomized phase II comparison of standard CHOP with weekly CHOP in elderly patients with non-Hodgkin's lymphoma. *J Clin Oncol.* 1995;13:2386-2393.
52 Coiffier B, Haioun C, Ketterer N, et al. Rituximab (chimeric anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. *Blood.* 1998;92:1927-1932.
53. Coiffier B, Lepage E, Herbrecht R,et al. Mabthera (rituximab) plus CHOP is superior to CHOP alone in elderly patients with diffuse large B-cell lymphoma: interim analysis of a randomized GELA trial. *Blood.* 2000;96(suppl 1):223a. Abstract 950.
54. Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP: an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. *J Clin Oncol.* 1994;12:1169-1176.
55. Rodriguez-Monge E, Cabanillas F. Long-term follow-up of platinum-based lymphoma salvage regimens: the M.D. Anderson Cancer Center experience. *Sem Onc.* 1997;11:937-947.
56. Moskowitz CH, Bertino JR, Glassman JR, et al. Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. *J Clin Oncol.* 1999;17:3776-3785.
57. van Besien K, Rodriguez A, Tomany S, et al. Phase II study of a high-dose ifosfamide-based chemotherapy regimen with growth factor rescue in recurrent aggressive NHL: high response rates and limited toxicity, but limited impact on long-term survival. *Bone Marrow Transplant.* 2001;27:397-404.
58. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med.* 1995;333:1540-1545.
59. Philip T, Armitage JO, Spitzer G, et al. High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate grade or high-grade non-Hodgkin's lymphoma. *N Engl J Med.* 1987;316:1493-1498.
60. Blay J-Y, Gomez F, Sebban C, et al. the international prognostic index correlates to survival in patients with aggressive lymphomas in relapse: analysis of the PARMA trial. *Blood.* 1998;92:3562-3568.
61. Guglielmi C, Gomez F, Philip T, et al. Time to relapse has prognostic value in patients with aggressive lymphoma enrolled onto the PARMA trial. *J Clin Oncol.* 1998;16:3264-3269.
62. Przepiorka D, van Besien K, Khouri I et al. Carmustine, etoposide, cytarabine and melphalan as a preparative regimen for allogeneic transplantation for hig-risk malignant lymphoma. *Ann Oncol.* 1999;10:527-532.
63. Ratanatharathorn V, Uberti J, Karanes C et al. Prospective comparative trial of autologous versus allogeneic bone marrow transplantation in patients with non-Hodgkin's lymphoma. *Blood.* 1994;84:1050-1055.
64. Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced- intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. *Blood.* 2001;97:631-637.
65. Kottaridis PD, Milligan DW, Chopra R, et al. In vivo CAMPATH-1H prevents graft-versus-host disease following nonmyeloablative stem cell transplantation. *Blood.* 2000;96:2419-2425.
66. van Besien K, Kelta M, Bahaguna P. Primary mediastinal B-cell lymphoma: a review of pathology and management. *J Clin Oncol.* 2001;19:1855-1864.
67. Abou-Elella AA, Weisenburger DD, Vose JM, et al. Primary mediastinal large B-cell lymphoma: a clinicopathologic study of 43 patients from the Nebraska lymphoma study group. *J Clin Oncol.* 1999;17:784-790.
68. Bertini M, Orsucci L, Vitolo U, et al. Stage II large B-cell lymphoma with sclerosis treated with MACOP-B. *Ann Oncol.* 1991;2:733-737.
69. Todeschini G, Ambrosetti A, Meneghini G, et al. Mediastinal large B-cell lymphoma with sclerosis: a clinical study of 21 patients. *J Clin Oncol.* 1990;8:804-808.
70. Lazzarino M, Orlandi E, Paulli M, et al. Primary mediastinal B-cell lymphoma with sclerosis: an aggressive tumor with distinctive clinical and pathologic features. *J Clin Oncol.* 1993;11:2306-2313.

71. Nademanee A, Molina A, O'Donnell M, et al. Results of high-dose therapy and autologous bone marrow/stem cell transplantation during remission in poor-risk intermediate and high-grade lymphoma: international index high and high-intermediate risk group. *Blood.* 1997;90:3844-3852.
72. Sehn LH, Antin JH, Shulman LN, et al. Primary diffuse large B-cell lymphoma of the mediastinum: outcome following high-dose chemotherapy and autologous hematopoietic cell transplantation. *Blood.* 1998;91:717-723.
73. Zinzani PL, Martelli M, Magagnoli M, et al. Treatment and clinical management of primary mediastinal large B-cell lymphoma with sclerosis: MACOP-B regimen and mediastinal radiotherapy monitored by galium scan in 50 patients. *Blood.* 1999;94:3289-3293.
74. Popat U, Przepiorka D, Champlin R, et al. High dose chemotherapy for relapsed and refractory diffuse large B-cell lymphoma: mediastinal localization predicts for a favorable outcome. *J Clin Oncol.* 1998;16:63-69.
75. Stein H, Foss HD, Durkop H, et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. *Blood.* 2000;96:3681-3695.
76. Falini B, Pileri S, Zinzani PL, et al. ALK+ lymphoma: clinico-pathological findings and outcome. *Blood.* 1999;93:2697-2706.
77. Coiffier B, Brousse N, Peuchmaur M, et al. Peripheral T-cell lymphomas have a worse prognosis than B-cell lymphomas: a prospective study of 361 immunophenotyped patients treated with the LNH-84 regimen. *Ann Oncol.* 1990;1:45-60.
78. Cheng A-L, Chen YC, Wang CH, et al. Direct comparisons of peripheral T-cell lymphoma with diffuse B-cell lymphoma of comparable histological grades: should peripheral T-cell lymphoma be considered separately? *J Clin Oncol.* 1989;7:725-731.
79. Lippman SM, Miller TP, Spier CM, Slymen DJ, Grogan TM. The prognostic significance of the immunotype in diffuse large cell lymphoma: a comparative study of the T-cell and B-cell phenotype. *Blood.* 1988;72:436-441.
80. Kwak LW, Wilson M, Weiss LM, et al. Similar outcome of treatment of B-cell and T-cell diffuse large cell lymphoma: the Stanford experience. *J Clin Oncol.* 1991;9:1426-1431.
81. Armitage JO, Greer JP, Levine AM, et al. Peripheral T-cell lymphoma. *Cancer.* 1989;63:158-163.
82. Ansell SM, Habermann TM, Kurtin PJ, et al. Predictive capacity of the international prognostic factor index in patients with peripheral T-cell lymphoma. *J Clin Oncol.* 1997;15:2296-2301.
83. Melnyk A, Rodriguez A, Pugh WC, Cabannillas F. Evaluation of the Revised European-American Lymphoma classification confirms the clinical relevance of immunophenotype in 560 cases of aggressive non-Hodgkin's lymphoma. *Blood.* 1997;89:4514-4520.
84. Younes A, Cristofanilli M, McLaughlin P, et al. Experience with 9-cis retinoic acid in patients with relapsed and refractory non-Hodgkin's lymphoma. *Leuk Lymphoma.* 2000;40:79-85.
85. Dearden C, Matutes E, Catovsky D. Pentostatin treatment of cutaneous T-cell lymphoma. *Oncology (Huntingt).* 2000;14:37-40.
86. Kurtzberg J, Keating MJ, Moore JO, et al. 2-Amino-9-B-D-arabinosyl-6-methoxy-9H-guanine (9W 506U; compound 506U) is highly active in patients with T-cell malignancies: results of a phase I trial in pediatric and adult patients with refractory hematological malignancies. *Blood.* 1996;88(suppl 1):669a.
87. Dearden CE, Matutes E, Cazin B, et al. High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H. *Blood.* 2001;98:1721-1726.
88. Weisenburger DD, Armitage JO. Mantle cell lymphoma: an entity comes of age. *Blood.* 1996;87:4483-4494.
89. Hiddemann W, Unterhalt M, Herrmann R, et al. Mantle-cell lymphomas have more widespread disease and a slower response to chemotherapy compared with follicle-center lymphomas: results of a prospective comparative analysis of the German Low-Grade Lymphoma Study Group. *J Clin Oncol.* 1998;16:1922-1930.
90. Khouri I, Romaguera J, Kantarjian H, et al. Hyper-CVAD and high dose methotrexate/cytarabine followed by stem cell transplantation: an active regimen for aggressive mantle cell lymphoma. *J Clin Oncol.* 1998;16:3803-3809.
91. Freedman A, Neuberg D, Gribben J, et al. High-dose chemoradiotherapy and anti-B-cell monoclonal antibody-purged autologous bone marrow transplantation in mantle cell lymphoma: no evidence for long-term remission. *J Clin Oncol.* 1998;16:13-18.
92. Romaguera J, Dang NH, Hagemeister F, et al. Preliminary report of Rituximab with intensive chemotherapy for untreated aggressive mantle cell lymphoma [abstract]. *Blood.* 2000;96(suppl 1):3170.
93. Magni M, Di Nicola M, Devizzi L, et al. Successful in vivo purging of CD34-containing peripheral blood harvests in mantle cell and indolent lymphoma: evidence for a role of both chemotherapy and rituximab infusion. *Blood.* 2000;96:864-869.
94. Malone J, Molina, KE, Stockerl-Goldstein R, et al. Autologous hematopoietic cell transplantation for mantle cell lymphoma: the Stanford University/City of Hope experience [abstract]. *Proc Am Soc Clin Oncol.* 2001;20:49a.