Update on the Management of Follicular Lymphomas

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Author's disclosures of potential conflicts of interest are found on page 4 and at the end of this article.

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Abstract

Follicular lymphomas (FLs), the second most common type of non-Hodgkin lymphoma in the United States, are typically diagnosed in older patients. Grades 1 and 2 FLs, which account for about 75% of all FLs, are commonly indolent and incurable in most patients. Grade 3 FL is aggressive but may be curable. Diagnostic workup includes morphology, immunophenotyping, and, in some cases, molecular genetic analysis, cytogenetics or fluorescence in situ hybridization, and Ki67 testing. Staging workup includes physical examination, laboratory assessment, computed tomography scans, and bone marrow aspirate and biopsy. The Follicular Lymphoma International Prognostic Index allows stratification into low-, intermediate-, and high-risk disease and is widely used to predict outcomes and guide therapy. For patients with early-stage indolent FL, radiation therapy with or without systemic therapy is recommended. For those with advanced FL, observation is a common course of action since the goal of treatment is disease or symptom control. Once the decision to treat is made, several chemotherapy and immunotherapy regimens can be considered. Rituximab is a mainstay of treatment for indolent FL, and bendamustine is being studied alone or in combination regimens. Several novel agents, as well as hematopoietic stem-cell transplantation, are also under investigation. Side-effect prevention and management are essential for all patients undergoing FL treatment.

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The non-Hodgkin lymphomas (NHLs) are a heterogeneous group of malignancies with differing patterns of growth, expected response to treatment, and goals of therapy. In 2010, an estimated 65,540 new cases were diagnosed in the United States, making NHL the fifth and sixth most commonly diagnosed malignancy in men and women, respectively, and accounting for approximately 20,000 deaths (Jemal, Siegel, Xu, & Ward, 2010). Known risk factors for NHL include age; immunodeficiency states, such as acquired immunodeficiency syndrome; use of immunosuppressive agents by organ-transplant recipients or patients with autoimmune disorders; presence of infectious agents, including human T-cell lymphotropic virus type 1, Epstein-Barr virus, and *Helicobacter pylori;* and environmental exposures such as farming chemicals and Agent Orange (Lister, Coiffier, & Armitage, 2004).

Table 1. Follicular Lymphomas: Clinical Features and Treatment Goals

Grade 1	Grade 2	Grade 3
Predominantly small cells	Mixture of small and large cells	Predominantly large cells
Accounts for 40%–45% of FLs	Accounts for 30% of FLs	Accounts for 20% of FLs
Indolent	Indolent	Clinically aggressive
Generally incurable	Generally incurable	May be curable

Note. FL = follicular lymphoma. Information from Tan & Horning (2008).

Follicular lymphomas (FLs) are the second most common NHLs diagnosed in the United States, accounting for 22% of new cases (Armitage & Weisenburger, 1998). Follicular lymphomas are typically diagnosed in older populations, with a median age of 60 years at diagnosis (Tilly & Zelenetz, 2008). They are classified in the World Health Organization's classification system as grades 1 through 3, depending on the size of the malignant cells present (Tan & Horning, 2008) (Table 1). Grade 1 contains small cells, while grade 2 contains a mixture of large and small cells. Grades 1 and 2 FLs account for up to 75% of all FLs, are commonly indolent in their growth patterns, and are considered incurable in the majority of patients. Median survival is approximately 9 years after diagnosis, or 4.5 years after first relapse (Vitolo, Ferreri, & Montoto, 2008; Lunning & Armitage, 2007; Bendandi, 2008; Friedberg et al., 2009). Grade 3 FLs contain mainly large cells, have an aggressive clinical growth pattern, and may be curable using aggressive diffuse large B-cell lymphoma (DLBCL) treatment paradigms (Table 2). Grade 3 FL is subdivided into 3A or 3B according to the presence or absence of typical centrocytes, respectively (Ott & Rosenwald, 2008). Overall, the biology of grade 3 FL is not well understood, mainly because of its exclusion from both indolent FL and DLBCL clinical trials (Tilly & Zelenetz, 2008).

Table 2. First-Line Treatment of Diffuse Large B-Cell Lymphoma

Disease stage	Regimens
Localized disease (stage I, stage II nonbulky)	RCHOP × 3 cycles + RT RCHOP × 6 cycles ± RT If poor left ventricular function: RCEPP, RCDOP, RCNOP, DA-EPOCH+R, RCEOP
Advanced disease (stage II bulky or high risk, III, IV)	RCHOP × 6 cycles Clinical trial

Note. DA-EPOCH = dose-adjusted EPOCH; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; RCDOP = rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone; RCEOP = rituximab, cyclophosphamide, etoposide, vincristine, prednisone; RCEPP = rituximab, cyclophosphamide, etoposide, prednisone, procarbazine; RCHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCNOP = rituximab, cyclophosphamide, mitoxantrone, vincristine, prednisone; RT = radiation therapy. Information from NCCN (2011).

Diagnosis, Staging, and Prognosis

Patients with indolent FL typically present with painless lymphadenopathy (Tan & Horning, 2008). Incisional or excisional biopsy is the preferred method of obtaining diagnostic tissue, as fine-needle biopsies are often not adequate to determine the specific NHL subtype. Essential diagnostic workup on tissue samples includes morphology, immunophenotyping, and, in some circumstances, molecular genetic analysis, cytogenetics, or fluorescence in situ hybridization (FISH) for t(14;18), and Ki67 testing. Immunophenotyping commonly reveals CD19, CD20, CD22, and CD79 positivity. CD10 and CD23 may be positive or negative. CD5 and CD43 are negative and Bcl-2 is positive in the majority of cases of FL. There are reports indicating that a Ki67 proliferation fraction of > 30% may be associated with more aggressive clinical behavior, but no evidence suggests this should guide treatment decisions (Vitolo et al., 2008).

Staging workup includes a comprehensive physical examination, including symptom assessment; performance status; laboratory assessment; computed tomography scans of the chest, abdomen, and pelvis; and bone marrow aspirate and biopsy. A host of additional studies and considerations that may be appropriate based on pathologic and clinical findings include surface immunoglobulins, human leukocyte antigen-DR testing, lactate dehydrogenase (LDH), uric acid, hepatitis serologies, HIV antibody, beta$_2$-microglobulin, complete blood count with differential, comprehensive metabolic panel, and phosphorus (National Comprehensive Cancer Network [NCCN], 2011). Follicular lymphoma is staged as I–IV, with additional substaging based on extranodal disease (E), absence (A), or presence (B) of systemic symptoms and bulky disease, defined as any mass > 10 cm (X). Up to 85% of patients with indolent FL will be diagnosed with generally incurable stage III or IV disease, with fewer than 20% having B symptoms of fever, drenching night sweats, or unexplained weight loss ≥ 10%. The remaining 15% present with stage I or II disease, for which potentially curative treatment options may exist (Lister et al., 1989); see Table 3.

Table 3. Staging of Follicular Lymphomas

Stage	Description
I	Involvement of a single lymph node group
II	Involvement of multiple lymph nodes on the same side of the diaphragm
III	Involvement of multiple lymph nodes on both sides of the diaphragm
IV	Multiple extranodal sites or lymph nodes and extranodal disease
Substage	
E	Extranodal extension
A or B	Absence (A) or presence (B) of systemic symptoms
X	Bulky disease (mass > 10 cm)

Note. Information from Lister et al. (1989).

Despite improvements in diagnostic and staging technology, there remains wide disparity in the outcomes for patients with indolent FL. The Follicular Lymphoma International Prognostic Index (FLIPI) is widely utilized to project expected outcomes and to guide therapy considerations for patients newly diagnosed with FL (Solal-Celigny et al., 2004) (Figure 1). The FLIPI score allows stratification into low-, intermediate-, or high-risk disease and correlates with overall survival (OS). In addition to the clinically based FLIPI variables, a host of biomarkers are currently under investigation to improve the accuracy of predicting indi-

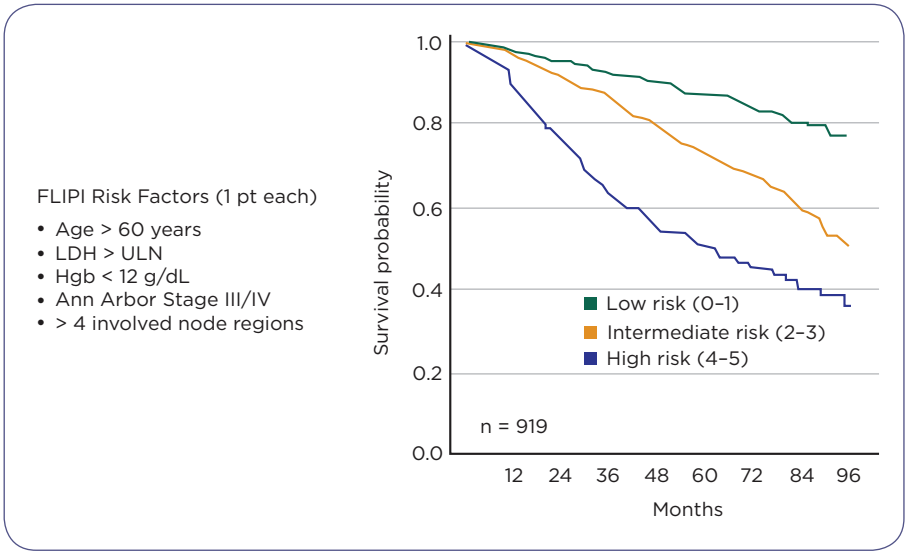

Figure 1. Follicular Lymphoma International Prognostic Index (FLIPI). Hgb = hemoglobin; LDH = lactate dehydrogenase; ULN = upper limit of normal. Adapted, with permission, from Solal-Celigny et al. (2004).

vidual patient outcomes (Cartron & Solal-Celigny, 2007; Relander et al., 2010).

Treatment

Treatment recommendations for patients with nonbulky, early-stage indolent FL commonly revolve around radiation therapy to involved fields, with or without systemic therapy, with the goal of long-term disease control or cure (Vitolo et al., 2008; NCCN, 2011). For the 85% of patients diagnosed with advanced-stage FL, observation is a common course of action, as the goal of treatment is disease and symptom control in the majority of cases. Observation is an option, based on four randomized trials showing no survival advantage for early chemotherapy compared with observation in asymptomatic patients (Ardeshna et al., 2003). In fact, only recently has any early evidence of improvement in survival been observed for patients with indolent FL; the increase in survival over the past 25 years is thought to be most likely due to improvements in treatment and supportive care (Swenson et al., 2005).

Modified Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria are typically used to guide timing of therapy initiation in patients with advanced-stage disease and include disease-related symptoms (not limited to B symptoms), threatened end-organ function, lymphoma-related cytopenia, bulky disease (single mass > 7 cm or > 3 masses > 3 cm), splenomegaly, and steady progression over at least 6 months. Patient preference and high FLIPI score may also be taken into consideration. Ideally, treatment for those not meeting GELF criteria is administered on a clinical trial (Brice et al., 1997; Tan & Horning, 2008; Vitolo et al., 2008).

If a patient meets GELF criteria and treatment is indicated, a host of chemotherapy and immunotherapy agents and regimens may be considered, based on the age and overall health of each individual patient (NCCN, 2011) (Table 4). In general, for both initial treatment and subsequent therapy, less aggressive regimens are reserved for the elderly or infirm. Since the goal of treatment is to control the disease while maintaining quality of life, however, every patient must be given individual consideration throughout all phases of their disease. After initial and second-line therapy, consolidation or extended dosing options are available, and autologous and allogeneic hematopoietic cell transplants (HCTs) are appropriate for select patients after second-line therapy.

Rituximab (Rituxan), an anti-CD20 chimeric monoclonal antibody, remains a mainstay in the treatment of indolent FL as a single agent, with radioimmunotherapy, as part of chemoimmunotherapy, or as an extended dosing option. Rituximab monotherapy in the setting of advanced-stage, asymptomatic disease is under much study. To date, no improvement in OS has been noted, and thus observation or enrollment in a clinical trial is the

Table 4. Therapy for Grades I/II Follicular Lymphomas[a]

First-line therapy	First-line therapy for elderly or infirm	First-line consolidation or extended dosing	Second-line or subsequent therapy	Second-line consolidation or extended dosing
Bendamustine+ rituximab RCHOP RCVP Fludarabine+ rituximab RFND Radioimmunotherapy Rituximab	If unable to tolerate first-line therapy, options: Radioimmunotherapy Rituximab (preferred) Single-agent alkylator ± rituximab	Chemotherapy followed by radioimmunotherapy Rituximab maintenance up to 2 yr	Any unused first-line options FCMR Radioimmunotherapy Any second-line option for diffuse large B-cell lymphoma	High-dose therapy with autologous stem-cell rescue Allogeneic stem-cell transplant for highly selected patients Rituximab maintenance up to 2 yr

Note. FCMR = fludarabine, cyclophosphamide, mitoxantrone, rituximab; RCHOP = cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab; RCVP = cyclophosphamide, vincristine, prednisone, rituximab; RFND = fludarabine, mitoxantrone, dexamethasone, rituximab.
Information from NCCN (2011).
[a] For patients with early-stage , locally bulky, or symptomatic disease, consider involved field radiation with or without systemic therapy.

primary recommendation for patients with asymptomatic, advanced-stage disease (NCCN, 2011; Tan & Horning, 2008; Vitolo et al., 2008).

Numerous randomized phase III trials have demonstrated improved response rates and superior progression-free survival (PFS) when comparing chemotherapy to chemotherapy with rituximab (Hiddemann et al., 2005; Foussard et al., 2005; Marcus et al., 2005; Herold et al., 2003). Extended dosing or maintenance rituximab doses and schedules have been widely studied (Table 5). In January 2011, based on data from the Primary Rituximab and Maintenance (PRIMA) trial, the US Food and Drug Administration (FDA) approved rituximab maintenance therapy for patients with previously untreated, CD20-positive FL who achieve a response to rituximab in combination with chemotherapy (Salles et al., 2011). Patients randomized to receive one dose of rituximab 375 mg/m^2 every 8 weeks for 24 months were noted to have superior remission depths and durations, with acceptable toxicity, when compared with patients being observed after receiving rituximab in combination with chemotherapy. Continued long-term follow-up is being conducted to determine whether improvement in PFS will correlate with improved OS.

With rituximab use on the rise, a host of trials have investigated rapid infusion schedules of 60 or 90 minutes vs. the traditional rate escalation used with 4- to 6-hour infusions (Atmar, 2010). All have concluded that initial infusions should continue to be undertaken slowly, per package insert, because of the high rate of cytokine release syndrome–related infusion reactions. Once good tolerance is established, however, rapid infusions have been found to be feasible and safe, with no impact on efficacy in both induction (rituximab with or without chemotherapy) and maintenance phases of treatment (Atmar, 2010). Chiang et al. (2010) also reported improved resource utilization for practice sites, as well as tangible time and cost savings for patients, by using a rapid rituximab infusion approach.

One of the most exciting agents since rituximab in the treatment arsenal for patients with FL is bendamustine (Treanda). Bendamustine, an alkylating agent with purine analog chemical properties, was approved by the FDA in 2008 for use in recurrent indolent lymphoma progressing ≤ 6 months after a rituximab-containing regimen (Cephalon, 2011). Kahl et al. (2010) studied bendamustine monotherapy and reported a 75% overall response rate (ORR: 14% complete response, 3% unconfirmed response, and 58% partial response) with a median duration of response of 9.2 months and an acceptable safety profile. Rummel et al. (2009) reported their randomized phase III trial of bendamustine and rituximab (BR) vs. cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and rituximab (RCHOP) in untreated follicular, indolent, and mantle cell lymphomas. Although ORRs were similar, length of response, time to next therapy, and side-effect profiles were favorable in the BR arm. Bendamustine monotherapy and combination regimens are currently being studied in a variety of malignancies. In addition, new agents with novel mechanisms of action are being widely investigated in FL (Leonard, 2010); see Table 6.

Hematopoietic cell transplantation is also an area of much study in FL. To date, three randomized trials evaluating autologous HCT have been reported (Tomblyn et al., 2011). All have shown high response rates and improved PFS, but only one reported improved OS. Unfortunately, relapse remains common after autologous HCT in contrast to allogeneic HCT, which is associated with lower relapse rates and potentially curative outcomes due to the graft-vs.-lymphoma effect and circumvention of tumor contamination associated with autologous harvests. However, overall

Table 5. Methods of Rituximab "Maintenance"

Author	Dosing	Frequency
Hainsworth, ECOG	4 weekly doses	Every 6 mo for 2 yr
Ghielmini	1 dose	Every 2 mo for 1 yr
Gordan	1 dose	Based on rituximab levels—monthly for 1 yr
ECOG	1 dose	Every 3 mo until relapse
BNLI	1 dose	Every 3 mo for 2 yr

Note. BNLI = British National Lymphoma Investigation; ECOG = Eastern Cooperative Oncology Group. Information from Hainsworth et al. (2002); Ghielmini et al. (2004); Gordan et al. (2005); Hochster et al. (2009); Van Oers et al. (2006).

Table 6. New Agents Being Studied for Follicular Lymphomas

Global target	Agent	Specific target
Cell surface		
• Anti-CD20	Ofatumumab	CD20
	Veltuzumab	CD20
	GA 101	CD20
	AME-133	CD20
• Other cell surface target	Epratuzumab	CD22
	TRU-016	CD37
	Milatuzumab	CD74
	Galiximab	CD80
	Blinatumomab	CD3 and CD19
• Immunoconjugates	Inotuzumab ozogamicin	CD22
	SAR3419	CD19
	^{90}Y-epratuzumab	CD22
Intracellular process		
• Proteasome inhibitors	Bortezomib	26S proteasome
	MLN9708	20S proteasome
	Carfilzomib	20S proteasome
• Bcl-2 inhibitors	AT-101	BH3
	ABT-263	Bcl-X_L
	Obatoclax	Bcl-X_L
• mdm2 inhibitors	Nutlin-3	p53
• Bcl-6 inhibitors	PU-H71	Hsp90
Cancer microenvironment	Lenalidomide	TNF, IL-6, IL-8, VEGF, T and NK cells
	Denileukin diftitox	CD25

Note. IL = interleukin; NK = natural killer; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor. Information from Leonard & Martin (2010).

disease benefit is offset by higher treatment-related mortality, and many reduced-intensity regimens are under study with the goal of reducing treatment-related mortality (Tomblyn et al., 2011).

Throughout any given patient's FL disease course, there is approximately a 30% incidence of disease transformation (Montoto et al., 2007; Al-Tourah et al., 2008). Transformation occurs when an aggressive NHL, most frequently DLBCL, arises from an indolent lymphoma. In patients with indolent FL, transformation should be suspected in the setting of rapid localized nodal growth, new onset of B symptoms, rapidly rising LDH, and new hypercalcemia. High-risk factors may include advanced disease stage, high FLIPI score at diagnosis, low hemoglobin, high LDH, and high FLIPI score at first recurrence. Biopsy should be pursued to confirm transformation whenever possible since median survival drops to 1.7 years, and treatment follows the paradigm of de novo DLBCL, including aggressive chemotherapy followed by autologous or allogeneic HSCT (Montoto et al., 2007; Al-Tourah et al., 2008).

Side-Effect Management

Because the majority of therapies used in the treatment of FL carry the risk of common yet significant toxicities—including myelosuppression, nausea and vomiting, bowel changes, anorexia, rashes, peripheral neuropathy, hyperglycemia, fatigue, infusion reactions and others—prevention and early treatment of side effects are imperative. One easily forgotten treatment side effect in patients with FL is tumor lysis syndrome (TLS), a life-threatening oncologic emergency. Tumor lysis syndrome results from the rapid destruction of tumor cells and is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, which can lead to renal failure, cardiac arrhythmias, and neuromuscular instabil-

ity. Disease, patient, and treatment factors impact a patient's overall risk of TLS (Table 7) and should be evaluated in all patients with FL when initiating a new treatment regimen. Outpatient prophylaxis and monitoring can easily be accomplished in appropriately identified high-risk patients (Goldman, Coiffier, Reiter, Younes, & Cairo, 2009).

Table 7. Risk Factors for Tumor Lysis Syndrome

Tumor	Patient	Treatment
WBC > 50,000	High uric acid at baseline	Chemotherapy
Highly proliferative tumors	Renal insufficiency (oliguria, dehydration, recent CT contrast)	Immunotherapy
Chemosensitive tumors	Catabolic state	Radiation therapy
Bulky tumors	Male gender	Corticosteroids
Extensive bone marrow involvement	Postmenopausal women	Hormonal therapy
Tumor invasion into kidney	Advanced age	
High LDH	Concurrent medications	

Note. CT = computed tomography; LDH = lactate dehydrogenase; WBC = white blood cell count.

Conclusion

The advanced practitioner (AP) in oncology is a critically important member of the health-care team for patients with FL. The individualized approach to both timing and choice of treatment, as well as the prevention and management of side effects, plays to the strengths of these roles. The chronic nature of the disease and the struggle to maintain a constant balance between disease control and quality of life are also factors well managed by the AP. Optimally, the number of new agents and treatment approaches available and under study will result in continued improvement in survival, making expertise in this group of diseases and management of these patients even more critical for oncology providers.

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REFERENCES

Al-Tourah, A. J., Gill, K. K., Chhanabhai, M., Hoskins, P. J., Klasa, R. J., Savage, K. J.,...Connors, J. M. (2008). Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. *Journal of Clinical Oncology, 26*(32), 5165–5169. doi:10.1200/JCO.2008.16.0283

Ardeshna, K. M., Smith, P., Norton, A., Hancock, B. W., Hoskin, P. J., MacLennan, K. A.,...Linch, D. C. (2003). Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: A randomised controlled trial. *Lancet, 362*(9383), 516–522. doi:10.1016/S0140-6736(03)14110-4

Armitage, J. O., & Weisenburger, D. D. (1998). New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *Journal of Clinical Oncology, 16*(8), 2780–2795.

Atmar, J. (2010). Review of the safety and feasibility of rapid infusion of rituximab. *Journal of Oncology Practice, 6*(2), 91–93. doi:10.1200/JOP.200001

Bendandi, M. (2008). Aiming at curative strategy for follicular lymphoma. *CA: A Cancer Journal for Clinicians, 58*(5), 305–317. doi:10.3322/CA.2008.0011

Brice, P., Bastion, Y., Lepage, E., Brousse, N., Haioun, C.,...Solal-Celigny, P. (1997). Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: A randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *Journal of Clinical Oncology, 15,* 1110–1117.

Cartron, G., & Solal-Celigny, P. S. (2007). Prognostic factors for lymphomas. In: R. Marcus, J. W., & M. E. Williams (Eds.), *Lymphoma: Pathology, diagnosis and treatment* (pp. 32–55). New York: Cambridge University Press.

Cephalon Inc. (2011). Treanda (bendmustine) prescribing information. Retrieved from http://www.treanda.com/pdf/TREANDA_final_PI.pdf

Chiang, J., Chan, A., Shih, V., Hee, S. W., Tao, M., & Lim, S. T. (2010). A prospective study to evaluate the feasibility and economic benefits of rapid infusion rituximab at an Asian cancer center. *International Journal of Hematology, 91*(5), 826–830. doi:10.1007/s12185-010-0583-z

Foussard, C., Colombat, P., Maisonneuve, H., Berthou, C., Gressin, R., Rousselet, M. C.,...Deconinck, E. (2005). Long-term follow-up of a randomized trial of fludarabine-mitoxantrone, compared with cyclophosphamide doxorubicin, vindesine, prednisone (CHVP), as first-line treatment of elderly patients with advanced, low-grade non-Hodgkin's lymphoma before the era of monoclonal antibodies. *Annals of Oncology, 16*(3), 466–472. doi:10.1093/annonc/mdi091

Friedberg, J. W., Taylor, M. D., Cerhan J. R., Flowers, C. R., Dillon, H., Farber, C. M.,...Link, B. K. (2009). Follicular lymphoma in the United States: First report of the national LymphoCare study. *Journal of Clinical Oncology, 27*(8), 1202–1208. doi:10.1200/JCO.2008.18.1495

Ghielmini, M., Schmitz, S. F., Cogliatti, S. B., Pichert, G., Hummerjohann, J., Waltzer, U.,...Cerny, T. (2004). Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. *Blood, 103*(12), 4416–4423. doi:10.1182/

blood-2003-10-3411

Goldman, S., Coiffier, B., Reiter, A., Younes, A., & Cairo, M. S. (2009). A medical decision tree for the prophylaxis (P) and treatment (T) of tumor lysis syndrome (TLS): An international TLS consensus panel [Abstract e17575]. *Journal of Clinical Oncology, 27*.

Gordan, L. N., Grow, W. B., Pusateri, A., Douglas, V., Mendenhall, N. P., & Lynch, J. W. (2005). Phase II trial of individualized rituximab dosing for patients with CD20-positive lymphoproliferative disorders. *Journal of Clinical Oncology, 23*(6), 1096–1102. doi:10.1200/JCO.2005.12.171

Hainsworth, J. D., Litchy, S., Burris, H. A., Scullin, D. C., Corso, S. W., Yardley, D. A.,...Greco, F. A. (2002). Rituximab as first-line and maintenance therapy for patients with indolent non-hodgkin's lymphoma. *Journal of Clinical Oncology, 20*(20), 4261–4267. doi:10.1200/JCO.2002.08.674

Herold, M., Dolken, G., Fielder, F., Franke, A., Freund, M., Helbig, W., & Pasold, R. (2003). Randomized phase III study for the treatment of advanced indolent non-Hodgkin's lymphomas (NHL) and mantle cell lymphoma: Chemotherapy versus chemotherapy plus rituximab. *Annals of Hematology, 82*(2), 77–79.

Hiddemann, W., Kneba, M., Dreyling, M., Schmitz, N., Lengfelder, E., Schmits, R.,...Unterhalt, M. (2005). Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood, 106*(12), 3725–3732. doi:10.1182/blood-2005-01-0016

Hochster, H., Weller, E., Gascoyne, R. D., Habermann, T. M., Gordon, L. I., Ryan, T.,...Horning, S. J. (2009). Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: Results of the randomized phase III ECOG1496 study. *Journal of Clinical Oncology, 27*(10), 1607–1614. doi:10.1200/JCO.2008.17.1561

Jemal, A., Siegel, R., Xu, J., & Ward, E. (2010). Cancer statistics, 2010. *CA: A Cancer Journal for Clinicians, 60,* 277–300. doi:10.3322.caac.20073

Kahl, B. S., Bartlett, N. L., Leonard, J. P., Chen, L., Ganjoo, K., Williams, M. E.,...Cheson, B. D. (2010). Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: Results from a multicenter study. *Cancer, 116*(1), 106–114.

Leonard, J. P., & Martin, P. (2010). Novel agents for follicular lymphoma. *Hematology, American Society of Hematology Education Program*. 259–264.

Lister, T. A., Crowther, D., Sutcliffe, S. B., Glatstein, E., Canellos, G. P.,Young, R. C.,...Tubiana, M. (1989). Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *Journal of Clinical Oncology, 7*(11), 1630–1636.

Lister, T. A., Coffier, B., & Armitage, J. O. (2004). Non-Hodgkin's lymphoma. In: M. D. Abeloff, J. O. Armitage, J. E. Niederhuber, M. B. Kastan, & W. G. McKenna (Eds.), Clinical oncology (pp. 3015–3058). Philadelphia, PA: Elsevier Churchill Livingstone.

Lunning, M., & Armitage, J. O. (2007). The curability of follicular lymphoma. *Transfusion and Apheresis Science, 37*(1), 31–35. doi:10.1016/j.transci.2007.04.012

Marcus, R., Imrie, K., Belch, A., Cunningham, D., Flores, E., Catalano, J.,...Smith, P. (2005). CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood, 105*(4), 1417–1423. doi:10.1182/blood-2004-08-3175

Montoto, S., Davies, A. J., Matthews, J., Calaminici, M., Norton, A. J., Amess, J.,...Lister, T. A. (2007). Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. *Journal of Clinical Oncology, 25*(17), 2426–2433. doi:10.1200/JCO.2006.09.3260

National Comprehensive Cancer Network. (2011). NCCN clinical practice guidelines in oncology: Non-Hodgkin's lymphomas. Retrieved from http://www.nccn.org/professionals/physician _gls/f_guidelines.asp

Ott, G., & Rosenwald, A. (2008). Molecular pathogenesis of follicular lymphoma. *Haemaologica, 93*(12), 1773–1776.

Relander, T., Johnson, N. A., Farinha, P., Connors, J. M., Sehn, L. H., & Gascoyne, R. D. (2010). Prognostic factors in follicular lymphoma. *Journal of Clinical Oncology, 28*(17), 2902–2913. doi:10.1200/JCO.2009.26.1693

Rummel, M. J., Niederle, N., Maschmeyer, G., Banat, A., von Gruenhagen, U., Losem, C.,...Brugger, W. (2009). Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent and mantle cell lymphomas: Final results of a randomized phase III study of the StiL (Study Group of Indolent Lymphomas, Germany) [Abstract 405]. *Blood, 114*.

Salles, G., Seymour, J. F., Offner, F., Lopez-Guillermo, A., Belada, D., Xerri, L.,...Tilly, H. (2011). Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial. *Lancet, 377*(9759), 42–51. doi:10.1016/S0140-6736(10)62175-7

Solal-Celigny, P., Roy, P., Colombat, P., White, J., Armitage, J. O., Arranz-Saez, R,...Montserrat, E. (2004). Follicular Lymphoma International Prognostic Index. *Blood, 104*(5), 1258–1265. doi:10.1182/blood-2003-12-4434

Swenson, W. T., Wooldridge, J. E., Lynch, C. F., Forman-Hoffman, V. L., Chrischilles, E., & Link, B. K. (2005). Improved survival of follicular lymphoma patients in the United States. *Journal of Clinical Oncology, 23*(22), 5019–5026. doi:10.1200/JCO.2005.04.503

Tan, D., & Horning, S. J. (2008). Follicular lymphoma: Clinical features and treatment. *Hematology Oncology Clinics of North America, 22*(5), 863–882. doi:10.1016/j.hoc.2008.07.013

Tilly, H., & Zelenetz, A. (2008). Treatment of follicular lymphoma: Current status. *Leukemia and Lymphoma, 49*, 7–17. doi:10.1080/10428190802311391

Tomblyn, M. R., Ewell, M., Bredeson, C., Kahl, B. S., Goodman, S. A., Horowitz, M. M.,...Laport, G. G. (2011). Autologous versus reduced-intensity allogeneic hematopoietic cell transplant for patients with chemosensitive follicular non-Hodgkin lymphoma beyond first complete response or first partial response. *Biology of Blood and Marrow Transplantation, 17*(7), 1051–1057. doi:10.1016/j.bbmt.2010.11.004

van Oers, M. H., Klasa, R., Marcus, R. E., Wolf, M., Kimby, E., Gascoyne, R. D.,...Hagenbeek, A. (2006). Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: Results of a prospective randomized phase 3 intergroup trial. *Blood, 108*(10), 3295–3301. doi:10.1182/blood-2006-05-021113

Vitolo, U., Ferreri, M., & Montoto, S. (2008). Follicular lymphomas. *Critical Reviews in Oncology/Hematology, 66*(3), 248–261. doi:10.1016/j.critrevonc.2008.01.014