Controversies in Follicular Lymphoma: "Who, What, When, Where, and Why?" (Not Necessarily in That Order!)

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Follicular lymphoma (FL) is the most common subtype of indolent lymphoma. Specific "facts" about FL that were generated by past research and have been passed down as dogma to a majority of practicing oncologists over the past 20 to 30 years that need to be revisited, include: (1) do not initiate therapy soon after diagnosis in asymptomatic, advanced-stage patients since it does not change outcome; (2) initiate therapy with single-agent oral alkylators when intervention needed and "save" more aggressive combination chemotherapy for "later" since the standard chemotherapy regimen used did not seem to impact survival; (3) FL is an incurable disease and palliation of symptoms was an acceptable approach to the expected pattern of repeated relapses; (4) transformation of FL is independent of the type or timing of therapies received by a patient; (5) median overall survival (OS) for FL patients is 8-10 years. Although the heterogeneity of FL will never change, we are developing the scientific tools to identify and better understand the biologic and genetic features associated with its clinical variability. In the current exciting era of targeted therapies (e.g., rituximab, radioimmunoconjugates) and novel treatment approaches demonstrating an improvement in treatment outcomes (e.g., disease-free survival and OS), our old beliefs and historically accepted dogma need to be retested and revitalized. The optimal combination(s) of old and new agents and the optimal timing of when to initiate and how to sequence specific therapies will require data from well-designed clinical trials that should include important correlative laboratory studies.

Follicular lymphoma (FL) is a neoplasm associated with follicle center B cells and typically contains the bcl-2 chromosomal translocation (i.e., t(14:18)), which leads to overexpression of the anti-apoptotic intracellular protein, Bcl-2. Bcl-2 protein overexpression is associated with drug-resistance (independent of p-glycoprotein) and prolonged cell survival. FL is the most common subtype of indolent (or low-grade) lymphoma. Specific "facts" about FL that were generated by past research and have been passed down as dogma to a majority of practicing oncologists over the past 20 to 30 years that need to be revisited, include: (1) do not initiate therapy soon after diagnosis in asymptomatic, advanced-stage patients since it does not change outcome; (2) initiate therapy with single-agent oral alkylators when intervention needed and "save" more aggressive combination chemotherapy for "later" since the standard chemotherapy regimen used did not seem to impact survival; (3) FL is an incurable disease and palliation of symptoms is an acceptable approach to the expected pattern of repeated relapses; (4) transformation of FL to an aggressive histological subtype resembling diffuse, large B-cell lymphoma (DLBCL) is independent of the type or timing of therapies received by a patient; (5) median overall survival (OS) for FL patients is 8-10 years. Although the heterogeneity of FL will never change, we are developing the scientific tools to identify and better understand the biologic and genetic features associated with its clinical variability. In the current exciting era of targeted therapies (e.g., rituximab, radioimmunoconjugates) and novel treatment approaches demonstrating an improvement in treatment outcomes (e.g., disease-free survival [DFS] and OS), our old beliefs and historically accepted dogma need to be retested and revitalized. It is likely that future treatment guidelines will be developed based on novel clinical (e.g., Follicular Lymphoma International Prognostic Index [FLIPI]), genetic (e.g., gene expression profile of tumor cells, immune response signatures), and biologic (e.g., adequate expression of the specific target recognized by a "target-specific" agent) features of each individual patient's tumor and host immune system. The optimal combination(s) of old and new agents and the optimal timing of when to initiate and how to sequence specific therapies will require data from a large number of well-designed clinical trials that should include important correlative laboratory studies. In addition, we need to identify and validate surrogate end-points in FL that will give us clinically meaningful data in a shorter period of time than OS.

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Who and When to Treat?

In this category, the less controversial FL subgroups and their corresponding timing of therapy would be: (a) Stage I or II FL (WHO follicular lymphoma, grade 1 or 2 through-

out this text, unless otherwise specified) diagnosed at presentation and treated with involved-field radiation therapy (IFRT), and (b) advanced-stage FL patients with progressive/symptomatic disease and treated with systemic therapy. For the relatively lucky 15% to 30% of FL patients to be diagnosed with stage I or II disease, upfront IFRT has been shown to give long-term local control and possible cure in a significant subset of patients.[1,2] More commonly, FL patients are found to have asymptomatic, advanced-stage disease at presentation. As mentioned above, few physicians would question the necessity of initiating therapy in those FL patients with symptomatic and/or rapidly progressive disease at time of diagnosis. However, the accepted and long-honored practice of watchful waiting of asymptomatic, advanced-stage FL patients needs to be reanalyzed and revalidated in today's era of targeted therapies. In the pre-rituximab era, standard chemotherapy-based treatments, whether single-versus multi-agent, (e.g., oral cyclophosphamide, cyclophosphamide + vincristine + prednisone [CVP], cyclophosphamide + hydroxydoxorubicin + oncovin + prednisone [CHOP], fludarabine ± mitoxantrone ± decadron, etc.) did not appear to change the natural relapsing history or OS of FL patients. Historically, patients with advanced-stage FL were found to have a median OS of 8 to 10 years.[3] The delay of "toxic" therapy until "needed" allowed patients to maintain a better quality-of-life by avoiding acute chemotherapy-associated side effects and perhaps even long-term toxicities by decreasing cumulative doses of drugs associated with the development of secondary myelodysplastic syndromes (MDS) or acute myelogenous leukemia (AML).

Now, time for some increasing controversy. In view of the ability to achieve prolonged (i.e., ≥ 5 years) remission duration from recent trials evaluating upfront immunotherapy/radioimmunotherapy alone or in combination with standard chemotherapy regimens brings the age-old practice of watchful waiting for the majority of asymptomatic FL patients into question yet again. Several important clinical trials addressing the issues of watchful waiting versus immediate treatment with "conventional" therapy need to be briefly revisited at this time. The US National Cancer Institute (NCI) enrolled a total of 104 advanced indolent lymphoma patients to a randomized clinical trial as follows: 44 were randomly assigned to "watch-and-wait"; 45 assigned to aggressive, upfront combination chemotherapy with prednisone, methotrexate, doxorubicin, cyclophosphamide, plus etoposide plus mechlorethamine, vincristine, procarbazine, prednisone (ProMACE-MOPP), followed by total nodal irradiation (TNI); and 15 "symptomatic" patients requiring therapy received the aggressive combination chemotherapy without randomization.[4] Notably, patients in the "watch-and-wait" arm could receive palliative RT to control localized progressive disease and remain on the "watch-and-wait" group. Nevertheless, initial results demonstrated OS at 5 years of greater than 75% in both arms, but 4-year DFS of 51% vs. 12% and "continuous" DFS of 51% vs. 0% were noted in favor of the initial aggressive therapy arm vs. watchful-waiting arm, respectively. As part of a commentary on a FL review article,[5] Longo offered an update to this NCI trial; he noted that in 1997, with a median follow-up of 13 years, no difference in OS was seen between arms; however, 75% of patients assigned to aggressive treatment who were alive were "continuously" cancer-free, in contrast to 75% of the patients in the watch-and-wait arm who were alive with lymphoma. Brice et al from Groupe d'Etude des Lymphomes Folliculares (GELF) randomized low-tumor-burden FL patients between initial watch-and-wait, predimustine (200 mg/m^2/day for 5 days per month × 18 months) or alpha-interferon (5 MU/d for 3 months, then 5 MU TIW × 15 months).[6] Deferred therapy was found to not adversely affect 5-year OS, which was 78%, 70% and 84% in arms 1, 2, and 3 respectively. However, neither single-agent predimustine or alpha-interferon would be considered as standard therapies for treatment of FL by most practicing oncologists today. A large, multicenter trial done by the British National Lymphoma Investigation (BNLI) randomized 309 asymptomatic, advanced-stage indolent (204 FL) lymphoma patients between immediate chlorambucil therapy (up to 10 mg po qd until complete remission) to delayed chlorambucil therapy until clinical progression.[7] Of note, in both arms, the use of palliative, low-dose IFRT (1500-2000 Gy) to symptomatic lymphadenopathy was permitted. Following a median follow-up of 16 years, OS was similar in both groups (i.e., 5.9 years with immediate chlorambucil and 6.7 years with observation). Of interest was the observation that immediate therapy patients had higher CR rates (i.e., 63% CR) compared to delayed therapy patients (i.e., CR rate of 27%). One may question whether these data suggest that asymptomatic FL is more sensitive to oral alkylator therapy earlier on as compared to later on during its natural history. It is unknown whether a lower CR rate in watch-and-wait patients is associated with a reduced efficacy of subsequent therapies. Lastly, Peterson et al published a CALGB study in which 228 newly diagnosed stage III/IV follicular small cleaved cell (FSCC) and follicular mixed lymphoma (FML) patients were randomized between one of two immediate treatment arms: oral cyclophosphamide versus CHOP-Bleomycin combination chemotherapy.[8] No treatment advantage was seen in either group: at 10 years overall time to failure was found to be 25% versus 33% ($P = 0.107$) and OS of 44% vs. 46% ($P = 0.79$) in the oral chemotherapy versus CHOP-Bleomycin groups, respectively. Approximately 50% of the patients in both arms were asymptomatic. In an unplanned subgroup analysis, it was found that FML patients who received combination CHOP-Bleomycin had improvement in disease control and survival compared to patients treated with oral alkylator therapy. At the current time it would be extremely tedious, if not nearly impossible, to attempt to go back and re-examine individual patients and data from the aforementioned trials with respect to: reassigning pathology

using current WHO classification criteria; utilizing and documenting the same prognostic index (e.g., FLIPI) to all study patients in an attempt to ensure that we are comparing "similar" populations not only between studies, but also between treatment arms; not allowing patients that require IFRT for localized symptomatic disease to remain in the "observation" arm of a study since they are receiving "therapy"; apply the same definition for CR, "molecular" CR, partial response (PR), stable disease (SD), and progressive disease (PD) in all studies; and utilize the same restaging methods and schedule between all studies to guarantee conformity and allow a true analysis of outcome in FL to be generated from comparison of the data accrued in these earlier studies. Since these things cannot be done, I would like to make some basic observations and a simple quote which will attempt to tie together the overall results obtained from the above studies. First, the dramatic difference in prolonged "continuous" DFS in the immediate treatment arm of the NCI study at 13 years (51% compared to 0%) and the dramatically higher CR rate (63% compared to 27%) in relationship to immediate chlorambucil therapy in the BNLI study strongly suggest that asymptomatic FL is more sensitive to "upfront" therapy than to the same therapy given following a period of watchful waiting. A feasible explanation as to why OS was not impacted was that, in general, purely chemotherapy-based nonmyeloablative therapies lack "curative" potential. Secondly, the above studies were each important in their historic contribution to our knowledge-base relating to FL. With respect to today's novel target-specific therapies and encouraging results from recent immunochemotherapy and radioimmunotherapy trials, the results from earlier studies could be simply summed-up as follows: "**Suboptimal therapy in = suboptimal results out**." In order to help answer the original question: "Who and when to treat?" a large national/international watchful waiting versus immediate "immunochemotherapy-based" clinical trial of advanced-stage asymptomatic FL patients with monitoring of well-described clinical, laboratory, and pathological features is warranted. In fact, newly diagnosed FL patients with "good-risk" disease may eventually prove to be the optimal subset of FL to most benefit from today's novel biological-based treatment.

Why Treat FL?

Goals: palliation only or possible cure?

With improvement in treatment outcomes (i.e., long durable time-to-progression [TTP]; better "quality" CRs) being seen with current novel immunologic-based therapies, we need to rethink our goals associated with treatment of FL: (1) Palliation only? or (2) Potential "cure" in a subset of patients? Ultimately, "cure" where we envision eradication of all FL cells in a patient's body forever may not be achievable in this disease. If this statement is true, then our goal should not only be palliation of disease-associated symptoms, but "optimal" palliation by which patients receive therapies which induce long periods of durable remissions given in a way that limits unnecessary acute toxicity or risk of long-term toxicity (e.g., MDS, t-AML, secondary solid tumors), limits development of shared "cross-resistance" to other therapies, and sequenced in a way that any preceding therapy does not significantly preclude/limit the ability to use subsequent therapies (e.g., early autologous stem cell transplant and associated limited bone marrow reserve). Another important advantage associated with prolonged remissions between treatments is improvement in quality-of-life for patients in which fewer therapies are given over a specified period of time with less total time spent in hospitals, doctors' offices, and dealing with therapy-associated side effects, as well as a decreased rate of development of drug-resistance. However, for those of us who believe that in the rapidly advancing field of novel target-specific therapies and from an improved understanding of the biology of lymphoma, "cure" in at least good-risk subsets of FL treated early with immunochemotherapy-based treatments is an achievable goal in our lifetime.

Why is molecular monitoring of Bcl-2/IgH-positive cells by PCR important?

For cure to be possible, then "molecular" CR (i.e., clearing of Bcl-2 [14:18 chromosomal translocation]-positive cells from blood and marrow compartments as tested by sensitive polymerase chain reaction [PCR] assay), in addition to achievement of a "nodal" CR should become a requisite primary objective without which a "true" CR and potential cure is not achievable. A comprehensive article reviewing the significance of clinical and/or molecular remission, differences in a variety of PCR techniques utilized in monitoring cells bearing the t(14;18) or Bcl-2/IgH translocation, and limitations of molecular monitoring in FL has been recently published by Buckstein et al.[9] Although significant variability in results exists and is not surprising in view of the heterogenicity of FL natural history, differences in measurements and definitions of objective response (CR, PR, etc.), wide range of therapies utilized (oral alkylating agents to stem cell transplantation) and PCR methodology used, this article gives clear examples where: (1) prior randomized "chemotherapy-based" FL trials demonstrate that the achievement of a CR was independently associated with improved PFS and/or OS; (2) achieving a molecular remission (MR) (i.e., clearing of Bcl-2/IgH PCR signal from peripheral blood/marrow) after standard-dose chemotherapy, single-agent rituximab or immunochemotherapy, or autologous stem-cell transplantation has been associated with prolonged clinical remissions. Although several limitations of molecular monitoring are clearly recognized (**Table 1**), the importance of developing a world-wide, standardized PCR methodology that can be prospectively incorporated into clinical trials in an attempt to determine the prognostic value of molecular remission and its possible correlation with objective responses, progression-free survival,

Table 1. Limitations of polymerase chain reaction (PCR) molecular monitoring.

- Single, standardized, "clinically informative" PCR methodology is not currently in use
- Optimal timing and frequency of PCR testing is unknown
- Bcl-2 gene rearrangement can be found in the normal population (need to use quantitative "cut-off" points to limit false-positive results in serial follow-up of FL patients)
- Residual Bcl-2/IgH-positive cells may not be clonogenic cells or different clones may occur at different time-points

and OS cannot be understated. In the era of rituximab-based therapies, in which small numbers of circulating Bcl-2-positive cells in peripheral blood can be cleared with even a single infusion of rituximab, the following questions need to be addressed: (1) Will serial PCR testing of the bone marrow compartment be more "informative" and clinically meaningful than the peripheral blood compartment? (2) Which PCR technique (i.e., qualitative, semi-quantitative, or quantitative) and at what sensitivity will give us optimal "clinically-relevant" results? (3) Perhaps a negative PCR conversion in blood may prove to not be as important as: (a) The *inability* to convert from positive to negative PCR status; (b) Time from conversion to PCR-negativity back to positivity? and/or (4) Is unchanging low-level PCR-positivity as important as an increasing PCR "signal" in a quantitative assay which could serve as an early indicator for systemic tumor progression?

Why use anthracyclines as part of upfront therapy of FL?

Historically, anthracycline-based therapies have not been used as upfront therapy of FL by the majority of oncologists treating this neoplasm. Arguments proposed for "saving" anthracyclines for later in a patient's treatment course include: 1) delaying a patient's exposure to anthracycline-associated side effects (e.g., alopecia, nausea/vomiting, possible cardiotoxicity) since no survival advantage is seen with early use of anthracycline-based combination "chemotherapy" regimens; 2) "save" anthracyclines to use if and when a patient develops transformed large B-cell lymphoma at a future date. Review of historical data from two separate databases suggest upfront anthracycline-based aggressive therapy for FL may possibly decrease the risk of transformation of FL to more aggressive histologies. The NCI watch-and-wait versus aggressive combined modality treatment study when published in 1988[4] had a median follow-up of 4 years and was last updated in 1997 at a median follow-up of 13 years. An important finding in this study was the significantly lower rate of histologic progression in the group of patients randomly assigned to upfront anthracycline-containing aggressive primary therapy as compared to patients in the watch-and-wait group: 0% vs. 15% at 4 years, and 15% vs. 49% at 13 years ($P = 0.01$), respectively (personal communication, Dan Longo, MD, NIA). Independently, a recent large retrospective review of 260 patients treated on one of two consecutive phase II studies conducted at the British Columbia Cancer Agency (BCCA) demonstrates that use of an anthracycline-based aggressive regimen as initial treatment of indolent lymphoma is associated with a marked reduction in the risk of transformation.[10] In particular, Treatment 1: upfront BPVACOP (bleomycin, cisplatin, etoposide, doxorubicin, cyclosphosphamide, vincristine and prednisone) followed by IFRT ($n = 140$) was compared to Treatment 2: combination alkylator – purine analogue (cyclophosphamide – cladribine or fludarabine and prednisone) therapy ($n = 120$). With a long median follow-up of living patients of 90 months, transformed lymphoma was noted in 18% of patients receiving Treatment 1, compared to 27% in patients receiving Treatment 2. In addition, the 5-year risk of transformation for Treatment 1 was 9% compared to 24% for Treatment 2 ($P < 0.0095$); annual risk of transformation through 10-year follow-up was 1.5% versus 3.0%, respectively. Although there exist little data on the subject, it is theoretically possible that an alteration in cellular immunity following purine analogue therapy may have contributed to the increased risk of transformation seen in Treatment 2 patients. If aggressive anthracycline-based upfront therapy of FL proves to be associated with a lower incidence of lymphomatous transformation upon validation by additional retrospective analysis of large databases and prospective monitoring in future clinical trials, it may be explained by one of at least two possible scenarios:

1) A small subset of FL cells that represent transformed lymphoma cells are present at the time of diagnosis and their subsequent outgrowth is a direct consequence of the inability of palliative, nonanthracycline-containing therapies to eradicate them; and/or
2) Accumulation of genomic alterations in long-lived Bcl-2-positive cells and clonal selection may be responsible for transformation which can only be eradicated by anthracycline-based therapy and/or high-dose salvage therapy. The upfront use of aggressive anthracycline-based therapy as described above is likely associated with a significantly smaller (residual) tumor burden at risk over time for transformation as compared to patients delaying initiation of therapy because of watchful waiting and/or use of sequential non-anthracycline-containing "palliative" treatments.

It is also possible that the improved quality of tumor regression (i.e., achievement of "molecular," in addition to nodal CR) and prolongation of response duration achievable with upfront rituximab-based immunochemotherapy regimens (e.g., R-CVP versus CVP; R-CHOP vs. CHOP; R+F; concurrent R-FND) may give similar results with respect to a decreased risk of transformation as that associated with use of the more toxic, ProMACE-MOPP plus TNI or BPVACOP plus IFRT regimens described above.

Why consider continued inclusion of anthracyclines in current rituximab-based upfront immunochemotherapy regimens?

There are several reasons to include anthracyclines in rituximab-based upfront immunochemotherapy regimens:

1. *In vitro* laboratory data have demonstrated that rituximab provides synergistic antitumor activity with a number of chemotherapeutic agents, including cyclophosphamide, cisplatin, fludarabine and doxorubicin.[11,12]
2. Based on currently available response and follow-up data from upfront phase II R-CHOP,[13] phase III R-CHOP vs. CHOP,[14] and phase III R-CVP vs. CVP[15] clinical trials, the objective and complete response rates, along with durability of response, strongly suggest that R-CHOP is superior to R-CVP (see **Table 2**). Ultimately, results from a prospective, randomized study of R-CVP vs. R-CHOP will either confirm or refute these early observations.
3. For many physicians whose main concern about using anthracyclines upfront or early in the course of therapy for FL patients is anthracycline-associated toxicities, a potentially valuable, if not superior, alternative exists: pegylated liposomal doxorubicin (PLD). The "cardiac-sparing" nature of pegylated liposomal doxorubicin has been described in the literature.[16,17] Recently, the combination of PLD, vincristine and dexamethasone (DVd regimen) was found to demonstrate similar efficacy and less toxicity and supportive care in newly diagnosed myeloma patients, as compared to VAd in a phase III multicenter randomized trial.[18] Of note, in a multicenter phase II trial, single-agent PLD has demonstrated clinical benefit in patients with metastatic breast cancer previously treated with conventional anthracyclines.[19] In a phase I/II study of rituximab in combination with PLD in patients with refractory B-cell lymphoma that is nearing completion, this unique combination has been very well tolerated, not associated with cardiotoxicity (even in patients with up to 400 mg/m^2 of prior standard doxorubicin exposure or its equivalent), and associated with good antitumor activity.[20] If future lymphoma trials further validate these current findings, it is quite possible that PLD will someday replace doxorubicin or mitoxantrone as the anthracycline component-of-choice in combination chemotherapy regimens.

Table 2. Outcomes associated with R-CVP vs. R-CHOP.

	Clinical Trial		
Parameter	Phase III CVP	Phase II CHOP	Phase III CHOP
ORR	81%	100%	96%
% CR	41%	87%	20%**
TTP (median)	32 mos	82.3 mos	NR*

Abbrviations: R-CVP, Rituximab + Cyclophosphamide + Vincristine + Prednisone; R-CHOP, Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone; ORR, overall response rate; CR, complete response; TTP, time-to-progression

* Not reached at median follow-up of 20 months (i.e., 80% of R-CHOP patients still in remission)

** Discrepancy between CR rates noted from phase II vs. phase III R-CHOP trials are addressed later in this article and are likely secondary to differences in baseline prognostic factors and patient entry criteria

What to Use for Therapy at Presentation? At Time of Relapse?

It is beyond the scope or purpose of this brief article to even attempt to develop a "Table of Treatment Guidelines for FL." Before definitive guidelines can be developed, a significant amount of additional currently outstanding/unknown information with respect to gaining a better understanding of optimal antitumor activity for given subsets of FL patients, as well as the optimal "sequencing" of various treatment modalities (e.g., unlabeled mAbs, immunochemotherapy, radio-immunotherapy [RIT], vaccines, stem cell transplantation) to increase the durability of therapeutic responses needs to be acquired. At the current time, the "aggressiveness" of either initial or subsequent treatment is largely dependent on several factors: 1) tumor characteristics (rate of tumor growth, tumor size/bulk, etc.); 2) clinical/laboratory characteristics (e.g., FLIPI score; elevated β2-microglobulin); 3) patient characteristics (e.g., co-morbid medical problems, "goal of therapy," patient's wishes). An important step in this direction are recent publications that retrospectively evaluated prognostic factors associated with response to rituximab monotherapy[21-23] (**Table 3**) and the association of "high-risk" FLIPI score to "inferior" R-CHOP[13,24] treatment outcome. In addition, on review of the literature on RIT, it is quite evident that patients who achieve complete remissions (e.g., more prevalent in low-tumor burden and/or non-bulky disease) are the subgroup that achieve the most durable, long-term remissions from this treatment modality.[25,26] However, it is not enough for academic researchers to simply identify good and bad prognostic factors associated with a given treatment modality, but for the entire oncology community to incorporate this information into current clinical practice when making treatment decisions for patients.

Another potentially important factor to consider when discrepancies in treatment outcomes are seen following similar/identical therapy in separate trials is that of differences in inclusion/exclusion criteria between studies. This factor may quite possibly be responsible for the dramatic difference in CR rate (87% versus 20%, respectively) obtained from R-CHOP therapy from a phase II[13] versus phase III study[14] using the same tumor-response criteria. Differences in inclusion/exclusion criteria for the phase II versus phase III study are listed in **Table 4**. Forty-five percent of patients in the phase II study had good-risk, 32% intermediate-risk and 24% poor-risk FLIPI scores; compared to 14% low-risk, 41% intermediate-risk, and 45% high-risk

Table 3. Prognostic factor(s) versus outcome.

- Single 4-dose rituximab treatment for low-tumor burden follicular lymphoma (FL):[23]
  - o Median PFS: Better in low FLIPI (compared with intermediate or high FLIPI)
  - o Median PFS: Better in patients achieving molecular clearing of Bcl-2-positive cells by PCR
- Standard versus prolonged schedule rituximab ("Swiss-style"):[21]
  - o Independent prognostic factors for response (include):
    - Diameter < 5 cm
    - Follicular histology (versus mantle cell lymphoma)
    - Normal hemoglobin
    - Low lymphocyte count
  - o Independent prognostic factors for event-free survival:
    - Responded to induction
    - Stage ≤ III
    - FcγRIII v/v polymorphism
- Single 4-dose rituximab treatment in patients previously treated with chemotherapy (multivariate analysis):[22]
  - o Response to rituximab correlated with:
    - Follicular histology
    - Prior autologous BMT
    - Multi-agent chemotherapy
    - No bone marrow involvement
  - o Longer TTP and/or DR correlated with:
    - Low/normal serum LDH or Beta-2 microglobulin
    - High CD3-positive cells
    - Response to last chemotherapy

in the phase III study. Overall, the shortest TTP was seen in the poor-risk FLIPI group and similar "better" results were seen in the good, as well as the intermediate FLIPI groups in both sets of independent data bases. The phase III R-CHOP patients have a median follow-up of 20 months compared to a 9+ year follow-up in the phase II R-CHOP patients. I believe the waiting for "requirement for therapeutic intervention" (**Table 4**) quite likely put patients in the phase III study in a "worse" prognostic group and less sensitive to upfront R-CHOP therapy, which could explain the lower (i.e., 20%) CR rate. Furthermore, "better-risk" patients in the phase II study achieved unmaintained remissions (without secondary therapies such as alpha-interferon maintenance or autologous stem-cell transplantation utilized in the phase III study) from R-CHOP therapy alone for up to greater than 10 years in some cases. Another outstanding important question is whether rituximab "maintenance" therapy is needed following rituximab-based immunochemotherapy? Recent data suggest that it may improve outcomes in previously treated FL patients even after rituximab-based immunochemotherapy[27,28] (R-FCM [rituximab, fludarabine, cyclophosphamide, and mitroxantrone] or R-CHOP). The German R-FCM study of relapsed/refractory patients required the same "requirement for therapeutic intervention" as did the German phase III R-CHOP study. The EORTC 20981 R-CHOP study required that patients have refractory or recurrent disease after at least one,

Table 4. Pertinent inclusion/exclusion criteria for phase II and phase III R-CHOP (rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone) therapy.

A. Phase II Trial[13]
- Histologically confirmed low-grade or follicular B-cell lymphoma and measurable disease
- No prior chemotherapy or no more than 4 prior standard therapies (76% no prior therapy)
- "Bulky" disease (defined as any single mass > 10 cm in its greatest diameter) was excluded

B. Phase III Trial[14]
- Histologically confirmed, previously untreated, advanced-stage follicular lymphoma (grades 1 and 2)
- "Requirement for therapeutic intervention" (defined by one of the following):
  - o presence of B symptoms
  - o bulky disease (mediastinal lymphomas > 7.5 cm or other lymphomas > 5 cm in greatest diameter)
  - o impairment of normal hematopoiesis (hemoglobin less than 10 g/dL, ANC < 1.5×10^9/L, or platelet count < 100×10^9/L)
  - o rapidly progressive disease

but no more than two, nonanthracycline-containing chemotherapies and no prior exposure to rituximab. Although awaiting longer follow-up and final publication of the EORTC 20981 trial, data from these studies suggest an advantage to rituximab maintenance in previously treated patients with likely variable degrees of drug resistance. An important factor that needs to be monitored in these patients in the future is: "Responsiveness to next and subsequent therapies at relapse?" In an attempt to evaluate differences in the efficacy between different upfront R-chemo regimens (R-CVP, R-CHOP, R-FCM, R-MCP), as well as the potential impact (or not) of rituximab maintenance, an ongoing European intergroup study called PRIMA (Primary Rituximab and Maintenance) was initiated in January, 2006. The results from this important study are anxiously awaited. It is my opinion that low- or intermediate-risk FLIPI patients treated earlier in their course of disease with an effective biologically-based immunochemotherapy regimen (e.g., SWOG / CALGB / ECOG upfront R-CHOP vs. CHOP-Bexxar; R-FND; R-FCM) may achieve long-term unmaintained remissions that do not require the use of expensive maintenance and/or toxic myeloablative consolidative therapies (i.e., autologous stem cell transplantation).

Where?

Where are we now?

With respect to FL we are in a very exciting era of novel diagnostics, prognostics, and therapeutics that, although they can at times be confusing and tedious (and always controversial) have brought us to a "good" place where they can make a major impact in our understanding of FL. In fact, several recent publications are given here as direct or indirect evidence of positive feedback. In particular:

1) The 5-year relative survival rate in all races has statistically improved for NHL from 47% to 60% between 1974 to 1976 and 1995 to 2001[29] and likely is associated to the increasing use of novel biologics, in particular, rituximab.
2) Analysis of a large population-based registry of survival patterns among patients with FL has shown improved survival of these patients in the US.[30]
3) Evaluation of 4-year PFS/OS from a variety of CHOP-based clinical trials conducted by SWOG over the past several years demonstrated that the addition of an anti-CD20 antibody (i.e., sequential rituximab or post-chemotherapy ^{131}I-Tositumomab) improved 4-year PFS/OS as compared to earlier studies evaluating CHOP ± nonspecific immunostimulants.[31]
4) Evaluation of FFS and OS of advanced-stage FL versus treatment over time was reviewed by MDACC in 5 sequential cohorts of patients between 1972 and 2002.[32] It is their conclusion that the incorporation of biologic agents has led to significant outcome improvements in advanced-stage FL patients.[32]

Where are we going?

- The use of biomarkers to guide individualized FL therapy is not yet "ready for prime-time," but will likely be utilized in the future.
- Need to identify biomarkers that predict responsiveness to a given treatment modality so as to not waste valuable time, resources, and patient's quality-of-life with therapies that have little to no clinical efficacy.
- Ongoing research will continue to give us a better understanding of the molecular pathogenesis of FL and potentially identify additional novel molecular therapeutic targets.
- Prospective, gene expression profile analysis of FL patients participating in clinical trials is needed in an attempt to further validate and build on the current data suggesting that survival in FL is largely dependent on molecular features of tumor-infiltrating immune cells.[33]
- Retrospective and prospective use of molecular/cytogenetic markers (e.g., Bcl-2, CD10, MIB1) that may help clinicians predict "aggressiveness" of an individual patient's disease at any given time.
- With respect to the ever increasing number of antigens that are being targeted by monoclonal antibodies, a correlation between quantitative antigen density by flow cytometry[34] versus treatment outcome by a specific mAb therapy is needed. Development of a kit that could test several antigen targets at once and could guide the choice between one or several mAbs for an individual patient's lymphoma would be clinically useful.
- Prognostic indices will need frequent evaluation, validation, and changes as new treatment modalities are incorporated into treatment paradigms for FL since different factors may be negative with one form of therapy, but not another.
- Long-term follow-up of FL patients over time is critical so that we are not simply satisfied with short-term success with one therapy, while not looking at what impact it has upon responsiveness to future therapy. In addition to national and international study groups, the NCCN Lymphoma Outcomes Data Base and a large, Genentech-sponsored multi-institutional trial entitled "An Observational Study of Treatment, Outcomes, and Prognosis in Patients with FL," which follow FL patients longitudinally, will likely provide us with invaluable information as well.

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