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Dr. Joseph Connors is a clinical professor in the Department of Medicine, Division of Medical Oncology, at the University of British Columbia and the Chair of the Lymphoma Tumor Group for the British Columbia Cancer Agency.

Dr. Connors obtained his medical degree at Yale University, trained in internal medicine at the University of North Carolina in Chapel Hill, and completed his medical oncology fellowship with Dr. Saul Rosenberg at the Stanford University Medical Center from 1979 to 1981. He then joined the staff and faculty at the BC Cancer Agency and University of British Columbia and has focused his clinical activities and research efforts in the area of understanding lymphoid cancers.

Dr. Connors is best known for his clinical investigations into the treatment of Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemias and multiple myeloma. He serves as a member of the executive committee of the Hematology Site Group for the National Cancer Institute of Canada Clinical Trials Group, as chair of the Educational Affairs Committee of the American Society of Hematology and is on the scientific advisory boards of the Lymphoma Foundation Canada and the Lymphoma Research Foundation of the United States.

Dr. Connors has published over 200 peer-reviewed scientific articles addressing various aspects of research into lymphoid cancers. He has been awarded the Terry Fox Cancer Research Award by the British Columbia Medical Association, the Bernard L. Schwartz Memorial Award by the Scripps health system in San Diego, California, and the Canadian Cancer Society John W. Whittick Memorial Award by the Saskatchewan Medical Association.

This publication is a summary of a recent presentation by Dr. Joseph Connors, Clinical Professor in the Division of Medical Oncology at the University of British Columbia and Chair of the Lymphoma Tumor Group for the British Columbia Cancer Agency, Canada. He spoke to medical oncologists, haematologists and oncology registrars in Auckland, Hamilton, Wellington and Christchurch in November 2009, concerning the natural biology and treatment of follicular lymphoma.

Follicular lymphoma (FL) is the most common type of indolent non-Hodgkin's lymphoma (NHL). FL was originally described in 1938 as a single entity, Brill-Symmer's Disease or giant follicular lymphoma.[1] Since then, a wealth of data about its natural history lends confidence to the notion that this disease has been consistently and reliably identified by pathologists and that it is indeed a single entity. Another aspect of interest is that in 1938, it was noted that one of the major events that takes place in the evolution of FL is the development of a second lymphoma – the so-called transformation to diffuse large B-cell lymphoma (DLBCL) that can occur in this illness.

The lymphoma only occupies a part of the lymph node. Clinically, it presents with both peripheral and centriaxial lymphadenopathy. Bone marrow involvement is present in at least 50% of patients on initial diagnosis. The most common cytogenetic abnormality is t(14;18)(q32;q21), a translocation that results in the overexpression of the antiapoptotic protein BCL2. The *BCL2* gene is normally found on chromosome 18, and the translocation moves the gene into the immunoglobulin heavy chain locus on chromosome 14. FL can be distinguished from other morphologically similar lymphoproliferative disorders using immunohistochemical profiles; the expression of CD10+, CD19+ and CD20+ cells reliably predict the presence of FL. Flow cytometry reveals monoclonal surface immunoglobulin light chain expression (chain $\lambda$+ or $\kappa$+).

Although often referred to as an indolent lymphoma, it is important to note that FL is not a benign disease. In the USA, individuals aged between 60 and 69 years have a 1-year predicted mortality of nearly 3%, whereas the likelihood of dying within the next year (starting from the date of diagnosis) is 26% for those in the same age group who are diagnosed with indolent lymphoma [see Figure 1].[2] This constitutes about a third of the lymphomas seen in North America and in most populations derived from European genetic stock; New Zealand would be expected to be similarly affected.

The province of British Columbia (BC) encounters approximately 120 new FL cases annually, within a population of 4.3 million individuals. Typically, about 90% of cases present with advanced-stage disease (widely disseminated) and 10% with limited-stage disease (curable). In Canada, the lifetime risk for developing FL is 1 in 200. The aetiology remains unknown. Highly effective treatments exist; chemotherapy and radiation response rates exceed 90%, but the disease remains incurable. More than 70% of patients will be progression-free for 2–4 years; this period has not yet been successfully prolonged.

| Age group | U.S. population expected %1-yr mortality | Indolent lymphoma mortality |
|---|---|---|
| 60-64 | 1.62 | 29.5 |
| 65-69 | 2.60 | 26.0 |
| 70-75 | 5.33 | 45.1 |
| **> 75** | 6.87 | 65.9 |
| Overall | 2.52 | 32.1 |

**Figure 1. Indolent lymphoma: age-adjusted mortality vs normal[2]**

## Myth 1. Treatment outcome has not changed

This statement is often based on data such as those published by Horning and colleagues in 1993, who analysed survival data from patients with indolent lymphoma spanning three different periods, 1960–1975, 1976–1986 and 1987–1996, during which three different treatment protocols were used at Stanford University.[3] Overall survival (OS) curves were not discernibly different between the three time periods. However, an analysis of survival data from large cohorts of patients with FL treated in BC reveal an approximately 33% decrease in 10-year mortality when patients treated in the 1980s are compared with those treated in the 2000s [see Figure 2]. Such data are not isolated to BC; data from three different protocols administered by the Southwest Oncology Group from 1974–2004 reveal a progressive improvement in OS by treatment strategy, with 4-year OS estimates of 69% for CHOP alone, 79% for ProMACE, and 91% for CHOP+MoAb (e.g. rituximab).[4] Similarly, MD Anderson data from the period 1977–2003 demonstrate improvement in survival of stage IV indolent NHL, with intensification of treatment regimens.[5] Thus, treatment is changing the natural history of FL and substantially improving outcomes for these patients.

## Myth 2. Limited-stage disease is incurable

In long-term outcome data from BC involving 305 patients with low-bulk stage IA or limited IIA (≤3 contiguous nodal sites) presentation of FL who were administered involved field irradiation, about 50% of these patients relapsed over the 5–10 years after diagnosis. However, relapses have been infrequent for the remaining 40%–50% of patients beyond approximately 10 years of follow-up, indicating that this patient subgroup is curable.

Similarly, failure-free survival data published in 1991 by McLaughlin and colleagues regarding patients with stages I–II FL show that about 40%–50% of those who apparently have limited-stage disease can be cured with involved field irradiation.[6]

## Myth 3. We need a special prognostic scoring system

Many prognostic scoring systems have been developed to guide treatment, to help interpret clinical protocols and the results across trials, and to counsel patients. An international prognostic index (IPI) exists for DLBCL, one for mantle cell lymphoma, for T-cell lymphoma, for patients according to age groupings, and so on. How useful are all these prognostic systems?

Certain variables do carry prognostic weight for OS. For instance, the DLBCL IPI (also applicable to a wide variety of lymphomas of T- and B-cell type) comprises five prognostic factors, each of approximately equal weight; disease stage III or IV, age >60 years at diagnosis, performance status 2, 3 or 4, >1 extranodal sites, and a lactate dehydrogenase (LDH) level of >1. The IPI score has been proven to be a reasonably reliable predictor of patient survival in FL, as seen in data from a cohort of more than 1000 patients in BC and from 1403 participants in the International Lymphoma Study Group.[7] For both populations, OS rates differed among the various IPI risk groups. Thus, the IPI allows comparison of data across clinical trials.

An alternative to the IPI is the FLIP Index (Follicular Lymphoma International Prognostic Index) or FLIPI, developed for use in low-grade NHL. The FLIPI evaluates five variables (age, haemoglobin, LDH, Ann Arbor staging, number of nodular sites), yielding a potential for six risk group scores, ranging from 0 to 5. These scores can be sorted into three prognostic risk groups; a score of 0 or 1 is defined as "good", a score of 2 is "intermediate", while those scoring 3, 4 or 5 have "poor" survival probability.

Is this sufficiently additionally useful to justify having a separate scoring system? A comparison of these two systems demonstrates that three of the factors are identical; age, LDH, and stage. These factors make the most contribution to the eventual FLIPI score. For measuring the extent of disease, the IPI uses performance status and number of extranodal sites, whereas the FLIPI uses haemoglobin level and number of nodal sites. These latter variables contribute less to relative risk and are probably indirectly estimating the same sorts of factors.

## Justifications for using the IPI or FLIPI

For comparisons across clinical trials, the IPI serves a purpose. How do the prognostic indices perform in relation to guiding treatment, counselling patients and focusing clinical research? In regard to survival outcomes by
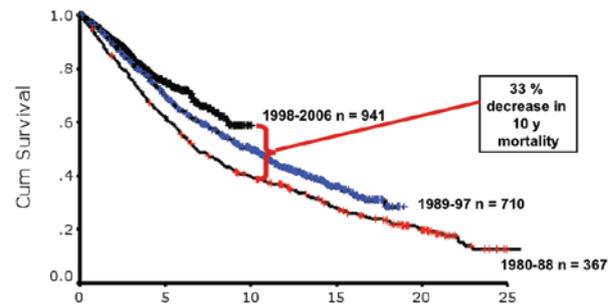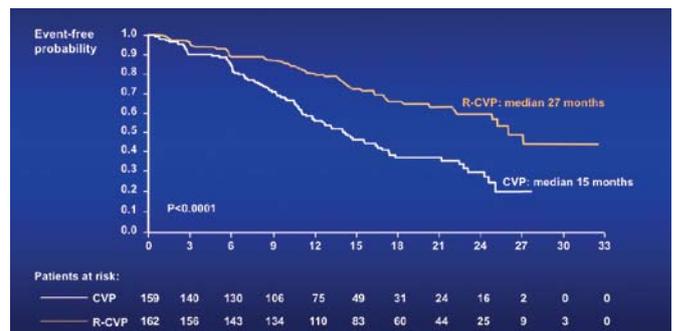


Figure 2. Follicular lymphoma in BC by era



Figure 3. R-CVP vs CVP alone in untreated advanced-stage FL: time to progression, relapse or death, final analysis (18 months' follow-up)

FLIPI prognostic groups, Solal-Céligny and colleagues report that after 6–7 years' follow-up, the high risk patients are still doing well.[8] If treatment was intensified in an attempt to improve outcome for these patients, it would need to be intensified for all and thereby potentially harm those 40%–50% who are going to do this well. In regard to those patients in the good prognostic risk category, might it be a good idea to reduce treatment intensity? Since approximately 10%–20% of these patients are already dying of their disease by 24–48 months' follow-up, this proposal is also unattractive. Dr. Connors therefore does not find the additional prognostic scoring provided by the FLIPI to be very useful; he prefers the IPI when describing FL.

## Myth 4. Rituximab is useful but it does not matter when it is given

Clinical data show that rituximab improves outcome for a number of B-cell malignancies, including FL, but the debate continues as to how much and when rituximab should be used. The Marcus M39021 study compared up to 8 cycles of CVP (cyclophosphamide, vincristine and prednisone) alone with CVP+rituximab (R-CVP) in 322 previously untreated patients with advanced-stage FL.[9] At the time of the final analysis, the median follow-up time in the overall population was 18 months [see Figure 3].[9] Compared with CVP alone, treatment with R-CVP was associated with a significant prolongation in time to treatment failure and time to disease progression or death (TTP) (p<0.0001). Notably, in further follow-up data regarding 26 of 94 patients on the CVP monotherapy arm that had started new treatment (13 received rituximab only and 13 received rituximab plus chemotherapy), TTP continued to show significant superiority for patients who had received rituximab as first-line therapy; subsequent administration of rituximab did not enable patients to achieve outcomes as favourable as seen in those given first-line rituximab.

Front-line rituximab therapy combined with 6–8 cycles of cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) similarly proved superior to CHOP alone for patients aged ≥60 years with untreated, advanced FL in the German Low-Grade Lymphoma Study Group (GLSG) trial.[10] Estimated 4-year PFS was 62% for R-CHOP and 28% for CHOP (p<0.0001). OS at 4 years was 90% with R-CHOP and 81% with CHOP alone (p<0.039). As with the Marcus M39021 study, the improvement in overall disease control was achieved by adding rituximab as part of the primary recipe; when missed out, the opportunity to gain the most benefit from rituximab was lost.

## Rituximab maintenance therapy highly beneficial

In the EORTC 20981 trial, patients with stages III or IV FL at initial diagnosis and relapsed after or resistant to non-anthracycline-containing systemic chemotherapy regimens received induction with either 6 cycles of 3-weekly CHOP alone or R-CHOP.[11] Responding patients underwent a second randomisation to either observation (no further treatment) or maintenance rituximab (375 mg/m$^2$ once every 3 months) until relapse or for a maximum of two years.

At 3 years' follow-up, CHOP and R-CHOP induction yielded similar OS rates (71.9% vs 82.5%; p=0.096). However, at a median follow-up of 6 years from start of maintenance treatment, rituximab resulted in a highly significant improvement of PFS: median 3.7 years versus 1.3 years in the observation arm (p<0.0001). The 3-year OS was 85.1% in the rituximab maintenance arm versus 77.1% in the observation arm (p=0.011). Notably, the advantage of rituximab maintenance for PFS was observed both after CHOP induction (p<0.0001) and R-CHOP induction (p=0.004).

Thus, rituximab appears to be effective as part of first-, second- and third-line treatment and until confirmed by further clinical studies, this protocol should be considered when rituximab is being used to treat FL, advises Dr. Connors.

## Myth 5. Rituximab is harmless

Rituximab therapy is associated with a number of potential risks, such as infusion-related toxicity, the reactivation/progression of some chronic infections such as hepatitis B and a possible association with progressive multifocal leukoencephalopathy (PML) [see Figure 4]. As a strategy to reduce the risk of reactivating hepatitis B, Dr. Connors uses prophylactic lamivudine concurrently with rituximab and for 6 months afterwards, even in patients whose disease is well controlled and in those who are currently asymptomatic. He suspects that the risk of PML may be greater as a result of the disease, rather than because of rituximab.

## Myth 6. All follicular lymphomas are alike

Over the years, nomenclature and classification of FL has evolved from the terminology used up to the 1950s, which described the giant follicular lymphoma as an early setting of lymphosarcoma, to the Rappaport classification in the late 1950s of "Diffuse, well differentiated", "Nodular, poorly differentiated", "Nodular, mixed" and "Nodular, histiocytic". This terminology has in turn been replaced by classification introduced by the Working Formulation ("Follicular, small cleaved", "Follicular, mixed" and "Follicular, large cell"), classified by the REAL/WHO as "Follicular, grades 1, 2, 3", respectively.

Debate continues as to whether a genuine difference exists: does "Follicular, large cell" lymphoma differ sufficiently in a biological fashion or according to treatment that would justify treating these patients differently? In the experience of Dr. Connors, survival in FL is similar regardless of subtype. The same disease-specific and OS outcomes are seen for both FL 3A and 3B. Thus, there seems to be no justification for incorporating these disease distinctions into treatment algorithms.

Dr. Connors endorses the *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* by Swerdlow and colleagues (http://www.who.int/bookorders) as an authoritative text for the classification of lymphomas. The 2008 edition has revised the old term "Follicular lymphoma with areas of DLBCL" to "Diffuse large B-cell lymphoma, with follicular areas", thereby switching the emphasis to highlight the dominant theme of the diffuse large B-cell lymphoma, signifying that this is the disease that requires the alteration in treatment. These follicular areas are reminders of an underlying FL, which may be expected to result in late relapses with indolent histology in patients, because lymphomas were present from the beginning. This new nomenclature may remove some of the controversy surrounding the follicular large cell type of lymphoma.

## Probe the biology

Recent insights into genetic and molecular aspects of FL may allow development of targeted therapies for disease categories and also underlie differences in the clinical course and outcome of FL. Besides molecular profiling identifying gene clusters associated with either favourable or poor prognosis, immunohistochemical studies have also defined the IPI as



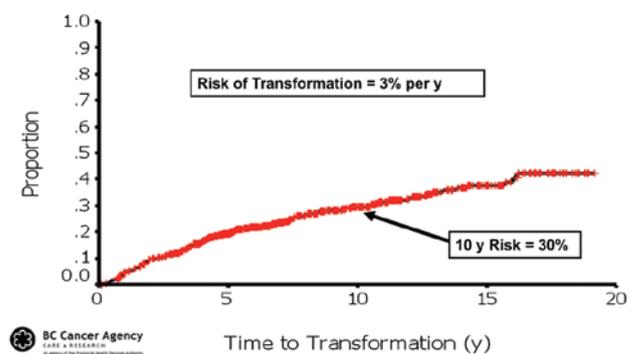Figure 4. Rituximab toxicity – observations



Figure 5. Indolent lymphoma risk of transformation. British Columbia experience (N=698)

an independent predictor of OS in FL patients. According to clinical data, lymphoma-associated macrophages (LAMs) as recognised by expression of CD68+ correlate with a poor prognosis; the lower the LAM score, the more favourable the outcome.[12] The expression of follicular FOXP3+ regulatory T cells is another immunohistochemical marker that acts as a predictive factor for PFS.[13] In a cohort of 102 patients, FOXP3+ expression pattern was associated with poor outcome: median PFS was 2.5 years for the 38 patients with a follicular architectural pattern, whereas PFS was a median 14.1 years for the 64 patients with a diffuse FOXP3+ expression.

## Myth 7. Patients die due to follicular lymphoma

As observed by Brill and Symmers in 1938, FLs are associated with the expression of transformed disease. Over time, cellular characteristics change in patients with FL, with the development of a second lymphoma – DLBCL. Biological correlates that accompany this transformation include mutational changes in expression of *P53*, 5'UTR *Bcl-6*, *Bcl-2*, P16 and *c-myc* gene activity, as well as secondary non-random cytogenetic changes.

Clinical data from BC patient cohorts show that approximately 3% of FL patients develop indolent lymphoma each year [see Figure 5]. Post-transformation OS rates are relatively poor; in a cohort of 85 FL patients administered CHOP therapy, 5-year OS was 33%. However, when indolent lymphoma survival is appraised from the date of FL diagnosis, survival curves extend for over a decade for those patients that never develop transformed disease – when it is noted that these patients are already in their 60s and 70s when diagnosed with FL, this survival is not vastly different from the normal expectation for the survival of the general population. The likelihood of staying alive is very much worse for those who ever develop transformed disease.

Adding rituximab to the CHOP regimen appears to be making a difference to post-transformation OS; preliminary data from a small number of patients show that 5-year survival exceeds 60% for patients receiving R-CHOP, versus approximately 30% for those given CHOP alone. Further data are awaited to confirm this finding.

## BC treatment algorithms

Dr. Connors discussed the overall management of FL, as followed by his practice [see Figure 6]. He emphasised that treatment decisions are largely tailored to individuals and that this depends greatly on the timing of the observation of transformed disease.

### Concluding remarks

Treatment outcome for FL has changed over the years, with improved treatment regimens increasingly extending survival for this disease. Up to 50% of patients with limited-stage disease survive beyond 10 years of follow-up and involved field irradiation has achieved cures in approximately 40%–50% of patients with stages I–II FL. It does matter as to when rituximab is administered; inclusion within primary treatment protocols leads to increased survival and extended rituximab therapy has been associated with improved outcome following chemotherapy or following rituximab induction. Re-use in maintenance further improves outcome. Rituximab has proven effective as part of first-, second- and third-line treatment. Rituximab can cause serious side effects. It is not the case that FL causes death – rather, it is secondary transformed DLBCL emanating from an indolent lymphoma that causes death.
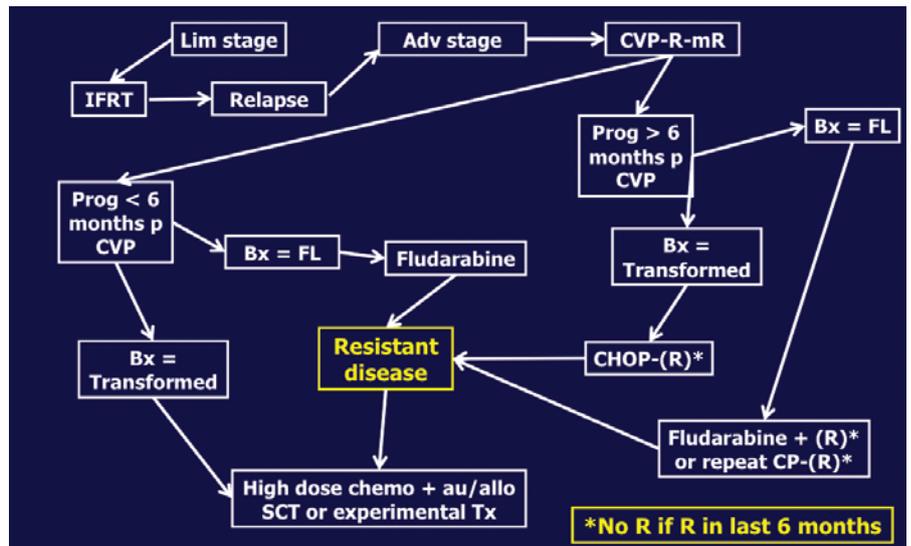


Figure 6. Follicular lymphoma: overall management

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