Treatment of early-stage follicular lymphoma: do as I say, not as I do

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Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin's Lymphoma (NHL), and the second most common type of NHL in the USA and Europe, accounting for nearly one-quarter of all new cases of NHL [1]. With the exception of patients with stage I disease, there is no established standard of care for the treatment of FL, and therapeutic approaches vary significantly worldwide [2]. The National LymphoCare Study provides a rich resource for the study of FL. It is a multicenter, longitudinal, prospective registry of 2728 patients with newly diagnosed FL enrolled between 2004 and 2007 from over 200 different community and academic practice sites in the USA [3]. The first publication from the LymphoCare Study in 2009 described current practice patterns for patients with newly diagnosed FL and revealed that a wide variety of therapeutic strategies are being used across the USA. These included observation in 17.7% of patients, rituximab monotherapy in nearly 14%, clinical trial referral in 6.1%, radiation therapy in 5.6%, chemotherapy only for 3.2% and chemotherapy plus rituximab in 51.9%. Among the 17% of patients with stage I disease enrolled on

this study, diverse treatment approaches were similarly observed, despite existing consensus guidelines recommending radiation therapy for patients with localized disease. Approximately one-third of patients were expectantly monitored, and another third received a rituximab-containing regimen (as either monotherapy or chemoimmunotherapy), but only approximately 25% of patients received standard radiotherapy. In a recent second analysis of the LymphoCare data to evaluate the outcomes of these early-stage patients, we found there were surprisingly no differences in overall survival (OS) between treatment groups, despite these varied treatment approaches. In fact, median OS was excellent, exceeding 80% at 5 years [4].

Recent data demonstrate that the OS of patients with FL is significantly longer than it was in previous years [5–7]. The LymphoCare study supports this, and suggests that for at least the small proportion of patients with localized FL, a hope for a prolonged disease remission can be sustained, and, most importantly, achieved through several means. The current literature guiding the management

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of early-stage FL was established in the pre-rituximab era, and is largely based on several single-center retrospective studies. Despite limitations of patient selection and heterogeneous radiation doses and delivery, these observational series showed that patients with early-stage FL treated with radiotherapy have OS rates of up to 80% at approximately 7–8 years, and similarly long relapse-free survival rates of up to 60% [8,9]. These studies provide the platform upon which both the European Society for Medical Oncology and the National Comprehensive Cancer Network recommend involved-field radiotherapy for patients with localized FL. Notwithstanding, the LymphoCare study found that only approximately 25% of patients received this treatment; rather, observation was the most common modality employed (30%). Given the excellent patient outcomes observed across all treatment modalities, and in the absence of robust prospective evidence to uphold any one therapeutic approach over another, the practicing oncologist is now challenged to maintain that radiation should remain the standard of care. What should then be made of existing recommendations?

The LymphoCare report sheds important light on the implementation of evidence-based practice. Clinical practice guidelines, such as those published by the National Comprehensive Cancer Network, are developed in alliance with leaders in the oncology field in an effort to sustain consensus-driven management and ensure that patients receive diagnostic, therapeutic and preventive services that are most likely to yield optimal outcomes. Yet, the low number of clinicians following existing treatment recommendations for localized FL suggests there may be limitations to the successful execution of these guidelines. Perhaps the biggest impediment lies in a lack of appreciation on the management of early-stage FL, given its rarity. This, coupled with poor underlying data to support existing guideline adherence, may explain the observed lack of execution. These limitations are not unique to oncologists and, in fact, are common across many medical specialties [10]. In a recent publication analyzing practice guidelines for NHL in The Netherlands, Wennekes and colleagues found a need to improve implementation in many areas encompassing both diagnosis and treatment [11]. Suboptimal adherence has been attributed to patient characteristics, such as age and comorbidities, tumor characteristics and variations in geographic practice patterns [11,12].

However, this may come at a price; one study evaluating quality of care in 1378 breast cancer patients found that better adherence to guidelines was related to superior OS and progression-free survival (PFS) [13,14]. In the LymphoCare study, differences in survival among patients with localized FL who underwent complete staging as dictated by practice guidelines were also noted [4]. Approximately 40% of patients underwent complete staging with bone marrow biopsies as well as diagnostic imaging with either a CT or (¹⁸F) fluorodeoxyglucose PET scan (referred to as ‘rigorously staged’ patients). Among these, rigorously staged patients had superior PFS compared with nonrigorously staged patients. While disease characteristics were similar between rigorous and nonrigorously staged patients, differences between these two groups of patients emerged across other categories. It appears that treatment selection may have been influenced by the degree of staging: more rigorously staged patients received chemoimmunotherapy or combined modality therapy (chemotherapy plus radiation) compared with nonrigorously staged patients ($p < 0.001$). In this group, fewer rigorously staged patients were expectantly observed compared with nonrigorously staged patients. These findings underscore the relevance and importance of complete staging of all patients with FL to maximize outcomes.

The LymphoCare study highlights that despite diverse approaches in the treatment of stage I FL outside of evidence-based recommendations, most patients enjoyed excellent outcomes. The corollary to this is that patients who did not undergo complete staging with diagnostic imaging and bone marrow biopsy, as benchmarks dictate, had inferior PFS.

Guidelines are clearly meant to promote quality of care and clinicians’ access to resources, and provide knowledge that can help guide decision-making in the management of cancer. Unfortunately, in the case of early-stage FL, our existing sources for those tools are outdated and potentially no longer relevant to the practicing clinician in today’s era of chemoimmunotherapy and emerging targeted therapies. The LymphoCare registry provides a prospective, robust and up-to-date source of data that we can capitalize on when making informed decisions on the management of rare cancers, such as early-stage FL. Large, randomized clinical trials in this setting are unlikely to happen largely because of cost and

long-term follow-up that would be required for this favorable group of patients. However, the comparative effectiveness research provided by the LymphoCare study is a reflection of standard practice from which we can extrapolate to complement existing data. Focused efforts to encourage broad participation in these types of studies should continue in order to replenish and update the sources we use to provide optimum patient care.

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