A Canadian Evidence-Based Guideline for the First-Line Treatment of Follicular Lymphoma: Joint Consensus of the Lymphoma Canada Scientific Advisory Board

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Abstract

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL) in North America. Because of the heterogeneity of the disease, treatment options vary from observation to aggressive therapies or stem cell transplantation, or both. Although advances in treatment have improved outcomes, the disease remains largely incurable. In Canada, no unified national guideline exists for the front-line treatment of FL; provincial guidelines vary and are largely based on funding. There is therefore a need for evidence-based national treatment guidelines that are supported by Canadian hematologists to ensure that patients with FL have equitable access to the best available care. A group of experts from across Canada developed a national evidence-based treatment guideline to provide health care professionals with clear guidance on the first-line management of FL. Results of a systematic review of the literature are presented with consensus recommendations based on available evidence.

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Introduction

Follicular lymphoma (FL) is the most common indolent (or low-grade) form of non-Hodgkin lymphoma (NHL) and the second most common form of all NHLs, composing up to 35% of all cases in North America and 9% to 22% worldwide.[1-5] In Canada, NHL was estimated to account for 4.2% of all new cancer cases in 2013.[6] Furthermore, between 1998 and 2007, there was a significant increase in the incidence rate of NHL in male patients (by 0.8% per year) and a numeric (but not significant) increase in female patients (by 0.4% per year).[6] In Canada, the incidence and prevalence of FL specifically are > 1500 cases and > 20,000 cases, respectively, per year.[7]

FL is staged using the Ann Arbor classification, in which stages I and II are considered limited or localized disease, and stages III and IV are considered advanced disease.[8] For all stages, patients presenting with traditional B symptoms (fever, night sweats, and weight loss) are considered symptomatic.[8] Other symptoms might include painful adenopathy/splenomegaly or locally obstructing symptoms. However, many patients, even some with advanced-stage disease, are asymptomatic. In addition to B symptoms, the Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria are commonly used to identify patients requiring immediate treatment.[4,9]

FL is further classified into histologic grades based on the World Health Organization (WHO) classification.[10] WHO categorizes FL into low grade (formerly grades 1 and 2) and high grade (previously grade 3a).[4,10] Diffuse areas in any grade 3 FL (previously grade 3b) should be designated as diffuse large B-cell lymphoma (DLBCL) and is typically treated as such. After diagnosis, the Follicular Lymphoma International Prognostic Index (FLIPI) and revised FLIPI2 may be determined for prognostic purposes.[11,12]

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Because of the heterogeneity of this disease, treatment options for patients with FL tend to be controversial and vary from observation (or "watch and wait") to stem cell transplantation (SCT).[13,14] With advances in treatment, patients with FL have shown improved outcomes; however, a curative treatment is still not available, particularly for advanced-stage disease.[4,13,15] Accordingly, the overarching goal of treatment is to achieve effective and durable disease control (ie, prolong overall survival [OS] and progression-free survival [PFS]) with minimal toxicity, while maintaining quality of life (QoL).[4,13,14]

Several international guidelines exist for FL, including the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), the British Committee for Standards in Haematology, the Italian Society of Hematology/Italian Society of Experimental Hematology/Italian Group for Bone Marrow Transplantation, as well as Spanish guidelines.[16-20] However, in Canada, there is no unified national guideline for FL. Although provincial guidelines exist, they differ across provinces and are primarily based on the availability of agents in the provincial formulary.[21,22] Accordingly, there is a need for evidence-based national treatment guidelines that are supported by Canadian hematologists to ensure that patients with FL in Canada have equitable access to the best available care.[23] Therefore, a group of experts from across Canada, including representation from Ontario, Quebec, Nova Scotia, British Columbia, and Alberta, developed a national evidence-based treatment guideline in association with Lymphoma Canada to provide health care professionals with clear guidance on the first-line management of patients with FL.

Target Population

The current guideline is for the primary treatment of adult patients with FL. Any patients with DLBCL or grade 3b FL should be treated according to DLBCL guidelines, and a discussion of their treatment is beyond the scope of this guideline.

Guideline Questions

1. What treatment options should be considered for localized FL?
2. How should asymptomatic advanced-stage FL be managed?
3. What treatment options should be considered for symptomatic advanced-stage FL?
4. In which patients should additional treatment be considered (ie, maintenance, consolidation, SCT)?

Methodology

When available, publications based on only phase III studies were included in the literature review. When few randomized trials were identified, we considered prospective studies. When few prospective studies were identified, we considered retrospective and institutional-level studies with a study sample of at least 20 patients. Publications in languages other than English were excluded. Relevant existing international practice guidelines from NCCN, ESMO, the British Committee for Standards in Haematology, the American College of Radiology, the Italian Society of Hematology/Italian Society of Experimental Hematology/Italian Group for Bone Marrow Transplantation, and Spain, as well as those from the Alberta Health Services, British Columbia Cancer Agency (BCCA), Cancer Care Nova Scotia, and Cancer Care Ontario, were also reviewed. Further details on methodology are included within each section of the guidelines that follow.

The expert panel used the NCCN categories of evidence and consensus to grade the level of evidence supporting recommendations.[24] Details of the NCCN categories are presented in Table 1.

Question 1: What treatment options should be considered for localized FL?

Background

Although the vast majority of patients are diagnosed with advanced FL, approximately 15% to 30% present with localized (stage I or II) disease.[25-27] Treatment of localized FL remains poorly defined and controversial because of a lack of randomized phase III trials in this uncommon subpopulation. Accordingly, based on data from retrospective series, radiotherapy (RT) is considered the standard of care for localized FL by North American and European guidelines, as well as provincial guidelines in Canada.[16-22] Alternative treatment options being examined in clinical trials include observation (ie, watch and wait [WW]) and combined modality therapies, such as chemotherapy or immunotherapy, or both, with and without RT. Furthermore, to the best of our knowledge, no current guidelines or literature distinguishes between asymptomatic and symptomatic localized FL; therefore, it is unclear if both presentations should be treated similarly.

Methodology

A literature search was performed using the following terms: follicular, indolent, lymphoma, stage I, stage 2, localized, limited, first-line, front-line, primary, asymptomatic, and symptomatic. When few randomized trials were identified, we considered prospective studies. When few prospective studies were identified, we considered retrospective and institutional-level studies with a study sample of at least 20 patients. Studies including patients with histologic types other than FL were eliminated from the literature review, with the exception of 1 study determined to be of key importance in determining the optimal dose of RT. All searches were limited to the years 2000 through 2014.

Radiotherapy

A total of 2 prospective and 10 retrospective studies examining RT in localized FL were found (Table 2).[25-35] In identified studies, the median age of patients with localized FL generally ranged from 50 to 64 years. Although a few studies reported that age was an independent prognostic factor for outcome, with younger age being

Table 1 NCCN Categories of Evidence and Consensus

Category 1	Based on high-level evidence, there is uniform consensus that the intervention is appropriate
Category 2A	Based on lower-level evidence, there is uniform consensus that the intervention is appropriate
Category 2B	Based on lower-level evidence, there is consensus that the intervention is appropriate
Category 3	Based on any level of evidence, there is major disagreement that the intervention is appropriate

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