Clinical Oncology xxx (2016) 1–16

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Guidelines

Rituximab in Lymphoma and Chronic Lymphocytic Leukaemia: A Practice Guideline

A. Prica [*], F. Baldassarre [†], L.K. Hicks [‡], K. Imrie [§], T. Kouroukis [¶], M. Cheung [§], the Members of the Hematology Disease Site Group of the Cancer Care Ontario Program in Evidence-based Care

[*] *Princess Margaret Hospital, Toronto, Ontario, Canada*
[†] *Program in Evidence-based Care, Cancer Care Ontario, McMaster University, Hamilton, Ontario, Canada*
[‡] *St. Michael Hospital, Toronto, Ontario, Canada*
[§] *Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada*
[¶] *Juravinski Cancer Centre, Hamilton, Ontario, Canada*

Received 12 April 2016; received in revised form 20 June 2016; accepted 5 July 2016

Abstract

Rituximab is the first monoclonal antibody to be approved for use by the US Food and Drug Administration in cancer. Its role in the treatment of non-Hodgkin lymphoma, including chronic lymphocytic leukaemia (CLL), has evolved significantly. We aimed to systematically review and update the literature on rituximab in lymphoma and CLL, and provide evidence-based consensus guidelines for its rational use. Validated methodology from the Cancer Care Ontario Program in Evidence-based Care was used. A comprehensive literature search was completed by a methodologist from the Hematology Disease Site Group of Cancer Care Ontario. Data were extracted from randomised controlled trials of rituximab-containing chemotherapy regimens for patients with lymphoma or CLL. Fifty-six primary randomised controlled trials were retrievable and met all inclusion criteria. Clinically important benefits in progression-free survival or overall survival were seen in the following settings: (i) addition of rituximab to combination chemotherapy for initial treatment of aggressive B-cell lymphomas, including diffuse large B-cell lymphoma, Burkitt lymphoma and HIV-related lymphoma with CD4 count $\geq 50/mm^3$; (ii) addition of rituximab to combination chemotherapy for initial and subsequent treatment of follicular lymphoma and other indolent B-cell lymphomas; (iii) use of rituximab maintenance in patients with indolent B-cell lymphomas who have responded to chemoimmunotherapy; (iv) addition of rituximab to fludarabine-based chemotherapy or chlorambucil for initial treatment of CLL. The consensus opinion of the Hematology Disease Site Group is that rituximab is recommended for these indications.

Key words: Chronic lymphocytic leukaemia; guideline; lymphoma; rituximab; systematic review

Introduction

Each year, over 2400 patients in Ontario are diagnosed with lymphoma. Indolent non-Hodgkin lymphomas (NHL), with follicular lymphoma representing the most common subtype, comprise 40% of lymphoma diagnoses and are incurable with conventional therapy. Patients often respond well to initial therapy with intravenous chemotherapy, which is associated with manageable adverse effects. However, later in the course of the disease, treatment involves more toxic intravenous chemotherapy, generally with a progressively shorter duration of response. The median survival in patients with advanced-stage disease is 7–10 years from the time of diagnosis. Diffuse large B-cell lymphoma (DLBCL) is the most common NHL worldwide, with follicular lymphoma a close second. Treatment comprises several cycles of intravenous chemotherapy, yielding cure rates of 60–70%. Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) is the most common type of leukaemia in the world, and its disease characteristics and treatment overlap with those of indolent lymphomas.

Author for correspondence: F. Baldassarre, Health Research Methodologist, McMaster University, Program in Evidence-based Care, Cancer Care Ontario, Hamilton, ON L8S 4L8, Canada. Tel: +1-905-527-4322x42834; Fax: +1-905-526-6775.
E-mail addresses: baldasf@mcmaster.ca, ccopgi@mcmaster.ca (F. Baldassarre).

http://dx.doi.org/10.1016/j.clon.2016.09.004
0936-6555/

Please cite this article in press as: Prica A, et al., Rituximab in Lymphoma and Chronic Lymphocytic Leukaemia: A Practice Guideline, Clinical Oncology (2016), http://dx.doi.org/10.1016/j.clon.2016.09.004

Monoclonal antibody therapy is a treatment approach being applied to lymphomas and other cancers. Rituximab is the first such agent to be approved for use by the US Food and Drug Administration and was approved in Canada in March 2000. However, this agent is expensive and has rare life-threatening, infusion-related toxicity. Phase II trials published in the late 1990s reported significant clinical activity and a favourable toxicity profile for this agent when used alone (e.g. [1]). Since this initial demonstration of benefit with rituximab monotherapy there has been an explosion of research detailing the use of rituximab and it has become standard of care in combination with chemotherapy in several types of lymphoma and CLL, as well as a maintenance strategy in indolent lymphomas.

When evidence of the single-agent activity of rituximab in lymphoma became available in 1998, the Hematology Disease Site Group (DSG) of Cancer Care Ontario's (CCO) Program in Evidence-based Care (PEBC) identified rituximab as a high priority. The DSG developed and regularly updated an evidence summary report [2] that later became a practice guideline, last updated in 2009.

We aimed to systematically review and update the literature on rituximab in lymphoma and CLL given many recent publications and updates, and provide evidence-based consensus guidelines for its rational use.

Materials and Methods

Guideline Development and Intent

The systematic review process was developed by the CCO-PEBC. The PEBC is supported by the Ontario Ministry of Health and Long-term Care. All work produced by the PEBC is editorially independent from the Ministry. This evidentiary base is composed of three parts: the evidentiary base of Version 2, the results of the updated search executed in March 2012 and the content of a further update executed in October 2013. Each of the searches was developed using a planned two-stage method and this document reports the methods used for the most recent update; methods for previous versions are very similar and are available upon request. The working group of the Hematology DSG comprising physicians with content expertise, epidemiologists and consumers developed this evidentiary base upon which these guideline recommendations are based.

Literature Search Strategy

For this update, a search for guidelines was undertaken in the Inventory of Cancer Guidelines (SAGE) (http://www.cancerguidelines.ca/Guidelines/inventory/index.php), the National Guideline Clearing House (http://www.guideline.gov/), the CMA Infobase (http://www.cma.ca/index.php/ci_id/54316/la_id/1.htm) and on the websites of international guidelines developers such as the National Institute for Clinical Excellence (UK) (NICE), the Scottish Intercollegiate Guideline Network (SIGN), the Australian National Health and Medical Research Council and the New Zealand Guidelines Group. The literature was systematically searched using MEDLINE (Ovid, March 2006 to October 2013), EMBASE (Ovid, March 2006 to October 2013) and the Cochrane Library (22 October 2013). In addition, abstracts from the American Society of Hematology (2006–2012) and the American Society of Clinical Oncology (ASCO) (2006–2013) were searched.

Study Selection Criteria and Protocol

This update review includes a search specific to Burkitt lymphoma and HIV-associated lymphoma, which were not included in the previous version. Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts in the English language comparing rituximab alone with non-rituximab regimens or comparing rituximab combination therapy with non-rituximab regimens and they were:

(i) Randomised controlled trials (RCTs), systematic reviews, meta-analyses, or evidence-based practice guidelines in lymphoma or CLL/SLL; other study designs such as prospective cohort studies and non-RCTs were considered for Burkitt and HIV-associated lymphoma.
(ii) Studies that included adult patients with lymphoma or CLL/SLL of any type, at any stage, and any histology;
(iii) Studies evaluating one or more of the following outcomes: overall survival, disease control (progression-free survival [PFS], event-free survival [EFS], time to treatment failure [TTF], or response duration), response rate, quality of life or toxicity.

The methodologist (FB) screened the titles and the abstracts of the citations identified by the electronic databases and the titles of the abstracts from ASCO and ASH conference proceedings, retrieved the full text of the selected articles and reviewed them, extracted data and created evidence tables. Ratios, including hazard ratios, were expressed with a ratio < 1.0, indicating that patients receiving rituximab had a higher probability of survival. All extracted data and information were audited by an independent auditor. Important quality features, such as required sample size and actual sample, loss to follow-up, blinding, randomisation method, allocation concealment, early termination, intention-to-treat analysis and ethical approval for each study were extracted.

Synthesising the Evidence

When clinically homogenous results from two or more trials were available, a meta-analysis was conducted using the Review Manager software (RevMan 5.2) provided by the Cochrane Collaboration [3]. For time-to-event outcomes, hazard ratios, rather than the number of events at a certain time point, were the preferred statistic for meta-analysis, and were used as reported. Statistical heterogeneity was calculated using the χ^2 test for heterogeneity and the I^2 percentage. A probability level for the χ^2 statistic $\leq 10\%$ ($P \leq 0.10$) and/or an $I^2 > 50\%$ was considered indicative of statistical heterogeneity.

Please cite this article in press as: Prica A, et al., Rituximab in Lymphoma and Chronic Lymphocytic Leukaemia: A Practice Guideline, Clinical Oncology (2016), http://dx.doi.org/10.1016/j.clon.2016.09.004