Evidence-based Series 6-2 EDUCATION AND INFORMATION 2014

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Treatment with Fludarabine for Patients With Follicular and other Low Grade Non-Hodgkin’s Lymphoma and Waldenstrom’s Macroglobulinemia

Members of the Hematology Disease Site Group

An assessment conducted in November 2013 put Evidence-based Series (EBS) 6-2 in the Education and Information section. (See the PEBC Assessment & Review Protocol for more information).

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

The reviewed EBS report, consists of

Section 1: Summary
Section 2: Full Report
Section 3: Guideline Review Summary and Document Review and Summary Tool

PG 6-2 consists of a Summary and a Full Report and is available on the CCO website (http://www.cancercare.on.ca) PEBC Hematology DSG page at: https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/hema-efs/

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For information about this document, the PEBC and/or the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

Guideline Report History

<table>
<thead>
<tr>
<th>GUIDELINE VERSION</th>
<th>SYSTEMATIC REVIEW</th>
<th>PUBLICATIONS</th>
<th>NOTES AND KEY CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original version</td>
<td>1985 – June 2001</td>
<td>Web publication</td>
<td>NA</td>
</tr>
<tr>
<td>June 2001</td>
<td>Full Report</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reviewed</td>
<td>2000- December 2012</td>
<td>Updated Web</td>
<td>2008 recommendations require</td>
</tr>
<tr>
<td>December 2012</td>
<td></td>
<td>publication</td>
<td>UPDATE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table of Contents

Guideline Summary..................................................................................................................3

Full Report................................................................................................................................7

Guideline Review Summary ......................................................................................................26

Document Review and Summary Tool ..........................................................................................28
GUIDELINE SUMMARY

Guideline Questions
1. What are the relative efficacy and other benefits of fludarabine compared with alternative options when treating patients with advanced-stage follicular and other low grade lymphoma and Waldenstrom’s Macroglobulinemia? Outcomes of interest include overall survival, progression-free survival, quality of life, and economic evaluations.
2. What are the toxicities of fludarabine?

Target Population
These recommendations apply to adult patients with stage III-IV follicular and other low grade lymphoma or Waldenstrom’s Macroglobulinemia who require therapy. Patients who require initial therapy, or who have been previously treated, are considered.

Recommendations
Previously Untreated Patients with Stage III–IV Low Grade Lymphoma
- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; or cyclophosphamide, doxorubicin, vincristine, and prednisone should be considered as first-line therapy, with the choice of treatment determined by patient preferences and clinical judgement. Choice of treatment should take into account factors such as route of administration, risk of infection, and outcomes of interest.

Previously Treated Patients with Stage III-IV Low Grade Lymphoma
- Fludarabine is an acceptable option for patients requiring treatment following disease progression after first-line therapy. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone; or rituximab may be appropriate alternatives. Choice of treatment should be determined by patient preferences, clinical judgement, and drug availability and should take into account factors such as the route of administration, the risk of infection, and outcomes of interest.

Patients with Waldenstrom’s Macroglobulinemia
- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients.
- Fludarabine is an acceptable option for patients previously treated with alkylator-based therapy who have relapsed or refractory disease.

Qualifying Statements
- Although the incidence of serious infections has been shown to be similar between patients treated with fludarabine and the combination of cyclophosphamide, vincristine, and prednisone, fludarabine significantly depresses T-cell-mediated immunity. Prophylaxis against pneumocystis carinii pneumonia with cotrimoxazole should be considered.
Autoimmune hemolytic anemia, a condition associated with lymphoma, may be exacerbated or precipitated by fludarabine and is considered by the manufacturer as a contraindication to the use of this drug.
The Canadian Blood Services and the British Committee for Standards in Hematology Blood Transfusion Task Force recommend that patients receiving, or who have previously received, fludarabine should receive gamma-irradiated blood products because of the risk of transfusion-related graft-versus-host disease.
Standard therapy with fludarabine consists of 25 mg/m² per day given intravenously for five consecutive days, for a total of six cycles, 28 days apart, or two cycles beyond maximum response.

Methods
Entries to MEDLINE (1985 through June 2001), CANCERLIT (1985 through March 2001), and Cochrane Library (1999 through Issue 2, 2001) databases and abstracts published in the proceedings of the annual meetings of the American Society of Hematology (1997-2000) and the American Society of Clinical Oncology (1997-2001) were systematically searched for evidence relevant to this practice guideline report. In addition, the Physician’s Data Query clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and PUBMED were searched.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative’s Hematology Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Hematology Disease Site Group, which is comprised of hematologists, medical oncologists, radiation oncologists, methodologists, and a patient representative.

External review by Ontario practitioners for all reports was obtained through a mailed survey. Final approval of all reports was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence
- Fludarabine has been compared with the combination of cyclophosphamide, doxorubicin, teniposide, and prednisolone, plus interferon, in a randomized trial involving 131 previously untreated patients ages 60-75 years, with follicular lymphoma and at least one high-risk feature. Patients receiving fludarabine had an inferior two-year time to treatment failure (49% versus 63%, p<0.05) and two-year survival (62% versus 77%, p<0.05).
- Fludarabine has been compared with the combination of cyclophosphamide, vincristine, and prednisone in a randomized trial reported in preliminary abstract form involving 309 previously untreated patients with diffuse small lymphocytic and follicular small cleaved or mixed cell lymphoma. Respective median progression-free survivals were 494 and 396 days (p value not given). Too few events had occurred to allow for an assessment of overall survival.
- Fludarabine has been compared with the combination of cyclophosphamide, vincristine, and prednisone in a randomized trial reported in preliminary abstract form involving 91 patients with low grade lymphoma who had previously received one to four treatment regimens. Patients receiving fludarabine had a superior two-year progression-free (32% versus 14%; p=0.028) and two-year treatment-free survival (41% versus 20%; p=0.034). No difference in two-year overall survival was detected (70% versus 75%; p=0.738). This study also assessed quality of life and demonstrated superior social function in patients receiving fludarabine.
Fludarabine has been compared with the combination of cyclophosphamide, doxorubicin, and prednisone in a randomized trial reported in preliminary abstract form involving 92 patients with Waldenstrom's Macroglobulinemia who were either refractory to or relapsed from initial alkylator–based therapy. Response was superior in patients receiving fludarabine (28% versus 11%; p=0.019). Superior progression-free survival in responding patients (p=0.02) and treatment-free survival in all patients (p=0.04) were also observed with fludarabine. No difference in survival was detected. Fludarabine was associated with less mucositis and alopecia; no differences in other toxicities were detected. Using a Q-TWIST analysis, patients receiving fludarabine spent more time without symptoms of disease or treatment toxicity (5.9 months; p=0.006).

Related Guidelines
The Practice Guidelines Initiative’s:
- Evidence Summary Report #6-8: Rituximab in Lymphoma.

For further information about this practice guideline report, please contact Dr. Ralph M. Meyer, Chair, Hematology Disease Site Group, Juravinski Cancer Centre, 699 Concession Street, Hamilton, Ontario, L3V 5C2; TEL (905) 575-7820; FAX (905) 575-6340.

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

Visit http://www.cancercare.on.ca/ for all additional Practice Guidelines Initiative reports.

PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.1 The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:
FULL REPORT

I. QUESTIONS
1. What are the relative efficacy and other benefits of fludarabine compared with alternative options when treating patients with advanced-stage follicular and other low grade lymphoma and Waldenstrom’s Macroglobulinemia? Outcomes of interest include overall survival, progression-free survival, quality of life, and economic evaluations.
2. What are the toxicities of fludarabine?

II. CHOICE OF TOPIC AND RATIONALE
Three hundred and fifty to 500 new cases of follicular and other low grade non-Hodgkin’s lymphoma are diagnosed in Ontario each year. This condition, while usually indolent, is not considered curable with currently available therapies. Treatment is aimed at controlling symptoms and prolonging survival. Options include observation, local radiotherapy, and oral chemotherapy with chlorambucil, prednisone, or more aggressive regimens that include cyclophosphamide, vincristine, and prednisone (CVP) or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Recent advances include the development of new agents that are active against lymphoma, including the purine analogues (fludarabine, cladribine) and monoclonal antibodies (rituximab). Although these agents show encouraging response rates in phase II trials, algorithms for treating patients with low grade lymphoma have not been clearly defined.

In 1994, the Hematology Disease Site Group (Hematology DSG) was asked by the Systemic Treatment Committee of Cancer Care Ontario (formerly the Ontario Cancer Treatment and Research Foundation) to consider developing guidelines for using fludarabine when treating patients with chronic lymphocytic leukemia (CLL) and lymphoma. This topic was considered as a potential priority because of uncertainties about the role of fludarabine in treating these conditions, observed variation in practice across Ontario, and high drug-acquisition costs. A practice guideline assessing the role of fludarabine in treating patients with CLL was completed (Practice Guidelines Initiative Practice Guideline Report #6-1: Fludarabine in Intermediate- and High-risk Chronic Lymphocytic Leukemia; http://www.cancercare.on.ca/access_1101.htm).

An initial draft of a guideline addressing the role of fludarabine in treating lymphoma was completed in 1995. At that time, studies testing fludarabine in lymphoma were all phase II design and restricted their assessments to response as the only clinical outcome. The DSG concluded that these data were insufficient to support a role for fludarabine as standard therapy for patients with lymphoma. This draft recommendation met with a low approval rating (58%) when circulated for practitioner feedback. Rather than attempting to redraft the guideline, the DSG elected to defer further consideration of this topic until the results of randomized trials became available. With the publication of randomized trials that assess progression-free and overall survival, and quality of life, this guideline has been re-evaluated.
III. METHODS
Guideline Development
This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario’s Program in Evidence-based Care (PEBC) using the methods of the Practice Guidelines Development Cycle (1). Evidence was selected and reviewed by two members of the PGI’s Hematology DSG and methodologists. Members of the Hematology DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on fludarabine, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy
An initial literature search was conducted in February 2000 and included the following databases: MEDLINE (1985 to February 2000), CANCERLIT (1985 to January 2000), and the Cochrane Library (Issue 4, 1999). The following terms were used for MEDLINE and CANCERLIT: “exp lymphoma”: (Medical subject heading (MeSH), title) combined with “fludara:” (title) or “fludarabine” (text word). The results were limited to human and English language. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/), PUBMED, and conference proceedings of the American Society of Hematology (ASH) and American Society of Clinical Oncology (ASCO) published in 1997-1999 were searched for reports of new or on going trials. Reference lists from relevant articles were searched for additional trials.

An updated literature search of the MEDLINE (March 2000 to June 2001) and CANCERLIT (March 2000 to March 2001) databases was conducted in June 2001. This update also included searches of the Cochrane Library (Issue 2, 2001), PDQ, and the 2000 ASH and 2000-2001 ASCO conference proceedings.

These same sources were searched to locate studies evaluating the role of fludarabine in Waldenstrom’s Macroglobulinemia. The search terms used in MEDLINE (1985 to June 2001) and CANCERLIT (1975 to March 2001) were: “exp waldenstrom macroglobulinemia”: (MeSH and title) combined with “fludara:” (title) or “fludarabine” (text word). The search was limited to human and English language. In addition to the 2000 ASH and 2000-2001 ASCO conference proceedings, the 1997-1999 proceedings were also searched for Waldenstrom’s Macroglobulinemia.

Article Assessment
Abstracts of relevant articles obtained from the February 2000 systematic literature search were blinded for author, institution, and whether the results were positive or negative. Two reviewers then independently assessed the blinded papers for inclusion. Reviewers were also unaware of whether the studies were published in journal or in abstract form. A Kappa of 0.7 or greater was predetermined to be acceptable. Where there was a discrepancy between the reviewers’ opinions, the reviewers discussed the individual blinded studies and decided whether to include
Inclusion Criteria
Articles were selected for inclusion in this systematic review of the evidence if they were one of the following:
1. Randomized controlled trials comparing fludarabine either as monotherapy or in combination with other treatment alternatives in patients with low grade lymphoma or Waldenstrom’s Macroglobulinemia. Primary outcomes of interest included survival, progression-free survival, or quality of life.
2. Reports of fludarabine-related toxicity in patients with low grade lymphoma or Waldenstrom's Macroglobulinemia.
3. Economic evaluations comparing fludarabine to other treatment alternatives in patients with low grade lymphoma or Waldenstrom’s Macroglobulinemia.

Exclusion Criteria
1. Trials of less than 10 patients (but individual case reports of toxicity were included).
2. Trials including fludarabine as part of a high-dose chemotherapy and/or transplant protocol.

Synthesizing the Evidence
Due to the heterogeneity of the treatment regimens compared with fludarabine, the varied use of fludarabine as either a single agent or as part of a combination regimen, and the lack of consistency in reporting the outcomes of interest, there was no attempt to pool efficacy data. Treatment-related toxicity data were summarized in the Adverse Events section of this document.

IV. RESULTS
Literature Search Results
A total of 151 citations were identified from the initial systematic literature search of February 2000, including 25 citations from the 1997-1999 conference proceedings. These citations were blinded with respect to author, site of work, citation, and results and were then independently reviewed by two members of the Hematology DSG. From these citations, 46 articles were considered to be potentially eligible for inclusion and were retrieved. The level of agreement by the Kappa statistic was 0.73. After further review of these 46 articles, 23 publications were assessed as meeting the eligibility criteria and included six randomized controlled trials (2-7), three economic evaluations (8-10), one quality of life analysis (11), and 13 toxicity reports (12-24). Of the six randomized controlled trials, four assessed previously untreated lymphoma patients (2-5), one assessed previously treated lymphoma patients (6), and one assessed patients with previously treated Waldenstrom's Macroglobulinemia (7).

The updated search of June 2001 identified an additional seven citations: three randomized controlled trials (25-27), two in previously untreated lymphoma patients (25,26) and one in previously treated lymphoma patients (27); one update reporting quality of life outcomes in a randomized trial assessing previously treated patients with Waldenstrom’s Macroglobulinemia (28); one economic analysis (29); and two toxicity reports (30,31).

Previously Untreated Patients with Low Grade Lymphoma
Six trials addressing fludarabine in previously untreated lymphoma patients (2-5,25,26) are included in Table 1. Two trials are restricted to older patients (2,4). Two are published in article form (2,5), and four are in abstract form (3,4,25,26).

Coiffier et al (2) reported the results of a randomized trial comparing fludarabine with cyclophosphamide, doxorubicin, teniposide, and prednisone plus interferon (CHVP-IFN) in 131 patients aged 60-75 years, with follicular lymphoma, and at least one high-risk feature. Risk
factors included B symptoms (fever, night sweats, and/or weight loss), an Eastern Cooperative Oncology Group (ECOG) performance status greater than 1, an increase in the serum lactate dehydrogenase (LDH) or β2 microglobulin level, or a specific criterion measure referred to as a high tumour mass. A high tumour mass was defined as a mass greater than 7 cm, large splenomegaly, the presence of an effusion, or a compressive tumour mass. Patients receiving fludarabine had an inferior two-year time to treatment failure (49% versus [vs.] 63%, p < 0.05) and two-year survival (62% vs. 77%, p < 0.05). Using the World Health Organization (WHO) Toxicity Scale, patients receiving CHVP-IFN experienced more grade 3-4 neutropenia. No differences were detected in episodes of infection. Patients receiving CHVP-IFN experienced more fatigue; 39% of patients receiving IFN either discontinued the drug or had dose modifications because of toxic reactions.

Table 1. Studies of previously untreated patients.

<table>
<thead>
<tr>
<th>Author (report)</th>
<th>Number</th>
<th>Patient Eligibility</th>
<th>Fludarabine Arm</th>
<th>Control Arm</th>
<th>Progression–Free Survival*</th>
<th>Overall Survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coiffer (2) (article)</td>
<td>131</td>
<td>Follicular lymphoma; Ages 60-75yrs., High risk disease†</td>
<td>Fludarabine: 25mg/m²/day x5days q28days x 6 cycles followed by 20mg/m² q2mos. x 6 cycles</td>
<td>CHVP: q28days x 6 cycles followed by q2mos. x 6 cycles; IFN 5 MU tiw x 18 mos.</td>
<td>FFS at 2 yrs.: 49% vs. 63% (p &lt; 0.05)</td>
<td>at 2 yrs.: 62% vs. 77% (p &lt; 0.05)</td>
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<tr>
<td>Hagenbeek (3) (abstract)</td>
<td>381</td>
<td>Low grade lymphoma; Stage III and IV</td>
<td>Fludarabine: 25mg/m²/day x5days q28days x 8 cycles</td>
<td>CVP: q28days x 8 cycles</td>
<td>Median: 494 vs. 396 days (p not stated)</td>
<td>Not reported</td>
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<tr>
<td>Foussard (4) (abstract)</td>
<td>100</td>
<td>Low grade lymphoma; Ages 55-75 yrs. Stage II bulky II, III-IV High risk disease‡</td>
<td>Fludarabine: 20mg/m²/day x5days q28days x 8 cycles</td>
<td>CHEP: q28days x 6 cycles followed by q2mos. x 3 cycles</td>
<td>Not reported</td>
<td>Not reported</td>
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<tr>
<td>Zinzani (5) (article)</td>
<td>199</td>
<td>Low grade lymphoma; Stage II - IV</td>
<td>Fludarabine: 25mg/m²/day x5days q28days x 6cycles</td>
<td>FI: q28 days x 6 cycles</td>
<td>at 36 mos..§: 56% vs. 90.5% (p=0.012)</td>
<td>at 42 mos.: 72.6% vs. 72.2% (p=ns)</td>
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<td>Tsimberidou (25) (abstract)</td>
<td>159</td>
<td>Indolent lymphoma Stage IV</td>
<td>FND: x 8 cycles + IFN/dex. x1year</td>
<td>ATT: x 12 cycles + IFN/dex x 1 year</td>
<td>At 5yrs.: 45% vs. 56% p=0.01</td>
<td>At 5 yrs.: 83% vs. 81% (p=ns)</td>
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<td>Bilgir (26) (abstract)</td>
<td>40</td>
<td>Low and intermediate grade lymphoma</td>
<td>Dose and schedule not stated</td>
<td>CHOP: schedule not stated</td>
<td>Not reported</td>
<td>Not reported</td>
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</table>

ATT=Alternating triple therapy; CHEP=cyclophosphamide, doxorubicin, vindesine, prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; CHVP=cyclophosphamide, doxorubicin, teniposide, prednisone; CVP=cyclophosphamide, vincristine, prednisone; FFS=failure-free survival; FI=fludarabine, idarubicin; FND=fludarabine, mitoxantrone (Novantrone®), dexamethasone; IFN=interferon; IFN/dex=interferon, dexamethasone; mos.=months; MU=million units; ns=not significant; q=every; tiw=three times per week; yrs.=years.
* Order of data provided is fludarabine vs. control arm
† High risk included any of B symptoms, ECOG performance status >1, increased LDH or β2 microglobulin, or high tumour mass
‡ High risk factors not stated
§ Progression-free survival reported only for responding patients
Hagenbeek et al reported in abstract form (3) the preliminary results of a randomized trial comparing fludarabine with CVP in 309 patients with diffuse small lymphocytic and follicular small cleaved or mixed cell lymphoma. Patients were stratified according to whether they needed therapy immediately upon diagnosis or had been previously observed off therapy. The dose of cyclophosphamide in patients receiving CVP was 750 mg/m² given intravenously. From an initial cohort of 381 patients, 72 (19%) were excluded after a central pathology review. The median progression-free survival was 494 days for patients receiving fludarabine and 396 days in those receiving CVP (p value not given). Too few events had occurred to allow for an assessment of overall survival. No differences in outcomes were detected when comparing subgroups of patients requiring initial therapy immediately after diagnosis and those who had been initially observed. Using the WHO Toxicity Scale, grade 2 or greater granulocytopenia and thrombocytopenia were more frequent in patients receiving fludarabine (p=0.001); significant alopecia occurred in the CVP group only.

Foussard et al reported in abstract form (4) the preliminary results of a randomized trial comparing fludarabine plus mitoxantrone (FM) with cyclophosphamide, doxorubicin, vindesine, and prednisone (CHEP) in 100 patients with low grade (excluding mantle cell) lymphoma. Eligible patients were 55-75 years of age with bulky stage II or stage III-IV disease and at least one high risk factor (not defined). Response to therapy was the only outcome reported, and only 68% of the patients accrued were evaluable for this endpoint. At one year, the response rate was superior in patients receiving FM (84% vs. 48%; p=0.023) with more complete responses (44% vs. 22%; p not indicated) apparent. Comparative toxicities were not described.

Zinzani et al (5) reported the results of a randomized trial comparing fludarabine with fludarabine plus idarubicin (FI) in 199 patients ages 25-65 years with low grade, including mantle cell, lymphoma. No differences in the respective response rates (84% vs. 81%) or survival at 42 months (73% vs. 72%) were detected (p values not given). Progression-free survival of all patients was not reported; the three-year progression-free survival in patients demonstrating a response to therapy was 90.5% in the FI group and 56% with fludarabine (p=0.012).

Tsimberidou et al reported in abstract form (25) the preliminary results of a randomized trial comparing fludarabine, mitoxantrone (Novantrone®), and dexamethasone (FND) with a multi-regimen combination, referred to as alternating triple therapy (ATT), in 142 patients with stage IV low grade lymphoma. Alternating triple therapy includes cyclophosphamide, doxorubicin, vincristine, dexamethasone, bleomycin, etoposide, cisplatin, cytarabine, mitoxantrone, prednisone, and procarbazine (CHOD-BLEO/ESHAP/NOPP). Eligible patients were less than 76 years of age and had documented adequate cardiac function. With a median follow-up of 56 months, five-year failure-free survival (FFS) was inferior in patients receiving FND (45% vs. 56% p=0.01); no difference in overall survival at five years was detected between FND and ATT (83% vs. 81%, respectively). There was more grade III-IV toxicity with ATT, including more frequent neutropenia (94% vs. 81%), thrombocytopenia (78% vs. 12%), and incidence of infection (27% vs. 12%).

Bilgir et al reported in abstract form (26) the preliminary results of a randomized trial comparing fludarabine with CHOP in patients with low and intermediate grade non-Hodgkin's lymphoma. There were 20 patients in each arm and response to therapy was the only outcome reported. Comparative toxicities were not described. Although a randomized trial, the outcomes reported were not sufficient for further consideration in this guideline.

Previously Treated Patients with Low Grade Lymphoma
Two of the three trials summarized in Table 2 evaluated fludarabine in previously treated patients with lymphoma (6,27).

Klasa et al reported in abstract form (6) preliminary results of a randomized trial comparing fludarabine with CVP in 91 patients with low grade lymphoma who had previously received one to four treatment regimens. Patients were required to have had a response to all previous
treatment courses; the dose of cyclophosphamide in patients allocated to CVP was 750 mg/m² given intravenously. Patients receiving fludarabine had a superior two-year progression-free survival (32% vs. 14%; p=0.028). The trial also assessed the time interval to requiring subsequent therapy (two-year treatment-free survival) and found this time was longer in the fludarabine group (41% vs. 20%; p=0.034). No difference in two-year survival was detected (70% vs. 75%; p=0.738). Patients receiving CVP experienced more nausea, vomiting, neurotoxicity, and alopecia. Patients receiving fludarabine experienced more infections; there were three treatment-related deaths in the fludarabine group but none attributed to treatment toxicity in patients receiving CVP. Quality-of-life outcomes assessed in this study were reported in a separate abstract (11), with superior social function observed in patients receiving fludarabine; no difference in other domains was detected. The authors attributed the improvement in social function to the lower incidence of nausea, vomiting, and alopecia in patients receiving fludarabine.

Tondini et al (27) reported the results of a randomized phase II trial comparing fludarabine with another purine analogue, cladribine, in 60 patients with relapsed or refractory low grade lymphoma. Responses were observed in 68% of patients receiving fludarabine and 72% of those receiving cladribine (p not given). The three-year progression-free survival in responding patients was 58% with fludarabine and 52% with cladribine (p not given). Cladribine was associated with a trend toward greater grade 3-4 neutropenia (66% vs. 50%; p not given) and more grade 3-4 thrombocytopenia (22% vs. 4%; p=0.05); the toxicity grading system was not defined. The authors concluded that both drugs were active, and that, given the observed myelosuppression, other doses and schedules of cladribine should be tested.

Table 2. Studies of previously treated patients.

<table>
<thead>
<tr>
<th>Author (report)</th>
<th>Patient Number</th>
<th>Patient Eligibility</th>
<th>Fludarabine Arm</th>
<th>Control Arm</th>
<th>Progression-Free Survival*</th>
<th>Overall Survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klasa (6) (abstract)</td>
<td>91</td>
<td>Low grade lymphoma; 1-4 prior regimens with response to all previous therapy</td>
<td>Fludarabine: 25mg/m²/day x 5 days q28days x 8 cycles</td>
<td>CVP: q21days x 4-10 cycles</td>
<td>at 2 yrs.: 32% vs. 14% (p=0.028)</td>
<td>at 2 yrs.: 70% vs. 75% (p=0.738)</td>
</tr>
<tr>
<td>Tondini (27) (article)</td>
<td>60</td>
<td>Diffuse small lymphocytic or follicular lymphoma; Relapsed or refractory to previous therapy</td>
<td>Fludarabine: 25mg/m²/day x 5 days q 1 mos.</td>
<td>Cladribine: 0.14mg/kg/day x 5 days q 1 mos.</td>
<td>At 3 yrs.: 58% vs. 52% † (p not stated)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Leblond (7) (abstract)</td>
<td>90</td>
<td>Waldenstrom’s Macroglobulinemia; Relapsed or refractory to alkylator therapy</td>
<td>Fludarabine: 25mg/m²/day x 5 days q28days x 6 cycles</td>
<td>CAP: x 6 cycles</td>
<td>Superior in fludarabine group† (p &lt; 0.05; data not stated)</td>
<td>Data not stated (p &gt; 0.05)</td>
</tr>
</tbody>
</table>

CAP=cyclophosphamide, doxorubicin (Adriamycin®), prednisone; CVP=cyclophosphamide, vincristine, prednisone; mos.=months q=every; yrs.=years

* Order of data provided is fludarabine vs. control arm
† Progression–free survival reported only for responding patients
Waldenstrom's Macroglobulinemia

One trial evaluating fludarabine in previously treated patients with Waldenstrom's Macroglobulinemia is summarized in Table 2 (7). No randomized trials involving previously untreated patients were identified.

Leblond et al reported in abstract form (7) the preliminary results of a randomized trial comparing fludarabine with cyclophosphamide, doxorubicin, and prednisone (CAP) in 92 patients with Waldenstrom's Macroglobulinemia that was either refractory to or relapsed from initial alkylator-based therapy. Response was superior in patients receiving fludarabine (28% vs. 11%; p=0.019). Superior progression-free survival in responding patients (p=0.02) and treatment-free survival in all patients (p=0.04) were also observed with fludarabine (data not provided). No difference in overall survival was detected (data not provided). Patients receiving CAP experienced more mucositis and alopecia; no differences in other toxicities were detected. In an updated abstract report of this study (28), the quality of life of the randomized groups was compared using ‘time without disease symptoms and toxicity’ (Q-TWiST) as the primary outcome measure. Patients receiving fludarabine had a mean gain of 5.9 months (p=0.006) of time without symptoms of disease or treatment toxicity, principally because of less time spent with relapsed disease.

Economic Evaluations

Four economic evaluations were identified and included one article (8) and three abstracts (9,10,29).

Sweetenham et al (8) reported the results of a cost-minimization analysis comparing CHOP, fludarabine, and rituximab in patients with relapsed indolent B-cell lymphoma. Costs of CHOP and fludarabine were assessed from a historical, single institution, cohort comparison; rituximab costs were assessed from a literature report of a multicentre phase II trial. Costs measured were for the acquisition of the antilymphoma medications and the management of treatment-related toxicity. The authors estimated the median costs to be £7,210 with CHOP, £10,022 with fludarabine, and £6,080 with rituximab. Response rates and median response durations were estimated to be similar across the three treatment groups. The authors suggested that the higher costs of fludarabine were due to higher drug-acquisition costs in comparison with CHOP, and greater costs in managing toxic events, in comparison with rituximab. The need to confirm these data in prospective randomized trials was stated. Hoffman LaRoche, a supplier of rituximab, sponsored this study.

Hieke and Kerrigan (9) estimated the costs of antilymphoma drug acquisition and the management of treatment-related toxicity of CVP, CHOP, and fludarabine by surveying 91 physicians from Canada, Germany, and Italy. Costs were obtained from a retrospective chart review of a single cycle of treatment for individual patients and then estimated over a median of six treatment cycles. Efficacy outcomes of therapy were not assessed. A direct comparison of the costs of each regimen was not provided. The authors concluded that the key determinants of cost were treatment schedule, therapy setting (in- vs. out-patient), and management of toxic events. Hoffman LaRoche sponsored this study.

Burchmore and Dowden (10) estimated the one-year costs of treatment in patients receiving fludarabine or rituximab. Rituximab costs were assessed from a phase II trial; fludarabine costs were estimated by considering published toxicity data. Efficacy outcomes were assumed to be similar. Costs for therapy at one year were estimated to be similar ($13,688 with rituximab vs. $13,121 with fludarabine). Genetech, a supplier of rituximab, sponsored this study.

Scott et al (29) estimated the costs of fludarabine and rituximab over a 13-month time period using data from 47 patients treated in Australia. A sensitivity analysis using varying estimates of in-patient needs and response was also included. The authors concluded that costs ($13,118 with rituximab and $12,919 with fludarabine) would be similar if response and in-patient admission rates were similar. Sponsorship of this study was not indicated.
Adverse Effects
Eight of the nine randomized trials reviewed above provided some description of treatment-related toxicities (2-7,25,27). In addition, 14 toxicity reports (12-22,24,30,31) and one phase I/II trial (23) were reviewed. Further toxicity data and references can be found in the Adverse Effects section of Practice Guideline Report #6-1: Fludarabine in Intermediate- and High-Risk Chronic Lymphocytic Leukemia (http://www.cancercare.on.ca/access_1101.htm).

Hematologic
Myelosuppression is a side effect of fludarabine. Profound lymphopenia and mild to moderate neutropenia and thrombocytopenia can occur. Although myelosuppression is the most common side effect, ECOG grade 3 or greater hematologic toxicity is seen in 3.8% and 5% of treatment courses in previously untreated lymphoma patients (2,5). When compared with CVP in previously untreated lymphoma patients, fludarabine was associated with more grade III-IV granulocytopenia (p=0.001) and thrombocytopenia (p=0.001) (3). When compared with CHVP-IFN, fludarabine appeared to be associated with less grade III-IV granulocytopenia (5% vs. 26% of patients), but the size of the study did not allow this potentially clinically important difference to achieve statistical significance (2).

In comparison with CVP in previously treated patients with lymphoma (6), and CAP in previously treated patients with Waldenstrom’s Macroglobulinemia (7), no differences in myelosuppression were observed.

Opportunistic infection
From the randomized trials, grade 3-4 clinical infection is observed in 1-2% of patients receiving fludarabine with no significant differences detected when compared with fludarabine plus idarubicin (5), CVP (3), or CHVP-IFN (2) in previously untreated lymphoma patients. In previously treated lymphoma patients, fludarabine was associated with more infections in comparison with CVP (6).

A retrospective case series assessing 2269 patients who received 7547 cycles of fludarabine reported a 3.2% incidence of opportunistic pulmonary infections (pneumocystis carinii pneumonia, candidiasis, mycobacterium avium intracellulare, aspergillus). Lack of prophylaxis was a predictor of the development of pneumocystis carinii pneumonia. Corticosteroid treatment before, during, or after fludarabine also increased the risk of opportunistic pulmonary infections (16). Cotrimoxazole prophylaxis for pneumocystis carinii pneumonia was included as part of the protocol in only one study (4); no cases of PCP were reported.

Autoimmune Phenomena
Autoimmune hemolytic anemia (AIHA) has been reported in as many as 7.5% of low grade lymphoma patients undergoing treatment with fludarabine (18); 50% of these patients had a history of AIHA. Unlike CLL, AIHA may correlate with disease progression in patients with low grade lymphoma (18). Because fludarabine has been reported to exacerbate or precipitate AIHA, the manufacturer considers AIHA to be a contraindication for using fludarabine (Practice Guideline Report #6-1). Autoimmune thrombocytopenia has also been reported (19).

Graft-versus-Host Disease
Transfusion-related graft-versus-host (GVH) disease has been anecdotally reported as occurring up to 11 months after treatment with fludarabine (14). The Canadian Blood Services and the British Committee for Standards in Hematology Blood Transfusion Task Force recommend that patients receiving, or who have previously received, fludarabine should receive gamma-irradiated blood products when these products contain viable lymphocytes (e.g., red cell or platelet concentrates) (15).
**Tumour Lysis Syndrome**

Although fludarabine-associated tumour lysis syndrome has been more typically described in patients with CLL, it has also been reported in low grade lymphoma (21).

**Neurological**

Peripheral neuropathy developed in 5 patients, all of which completely resolved within 5 weeks in one RCT (5) and was found to be more frequent with CVP in another (6). Five cases of unusual neurological illness were reported in fludarabine-treated patients with low grade non-Hodgkin's lymphoma (22). Neurological toxicity is dose limiting and the dose of fludarabine should not exceed the recommended dose (23).

**Other**

Nausea, vomiting, and mucositis are infrequent (5) and occur less frequently with fludarabine than with CVP (6). Fludarabine does not cause alopecia (5,6) and is not toxic to the kidneys or heart (5). Transient grade 2 hepatic toxicity has been observed (5). Individual cases of fatal fulminant myelofibrosis (12), fatal bone marrow necrosis (13), and seropositive symmetrical inflammatory polyarthritis (31) have been reported following fludarabine use in patients with indolent lymphoma. A single patient with low grade lymphoma was reported to have developed progressive epidermal necrosis following a second cycle of fludarabine; the syndrome was successfully treated with high dose steroids, cyclophosphamide, and immunoglobulins. (20). There have been individual case reports of Guillain-Barré syndrome in a patient with Waldenstrom’s Macroglobulinemia (30), fatal miliary tuberculosis in a patient with high grade lymphoma (17), and cryptococcal meningitis plus intracranial tuberculoma 18 months after completion of treatment in a patient with Waldenstrom’s Macroglobulinemia (24).

V. **INTERPRETIVE SUMMARY**

**Previously Untreated Patients with Low Grade Lymphoma**

Six randomized trials testing fludarabine in previously untreated patients with follicular and other low grade lymphomas were identified. Of these, two (2,3) compared fludarabine with a well-described standard therapy in an adequate number of patients and reported important efficacy outcomes that included at least progression-free survival, and in the case of one study, overall survival (2). These two studies were therefore used in determining guideline recommendations.

The trial comparing fludarabine with CHVP-IFN (2) was conducted in older patients with high-risk disease who are generally considered to be more susceptible to treatment-related toxicity. Despite the potential concern of treating these patients with an anthracycline regimen, superior outcomes, including survival, were observed in patients receiving CHVP-IFN. This study was given proportionately more weight in comparison with other studies as it was reported in full article form and found a survival difference between treatment groups (a difference in survival is rarely seen in randomized trials assessing patients with follicular and other low grade lymphoma). Issues related to contrasting CHVP-IFN to treatment regimens commonly used in Ontario, such as CVP or CHOP, were recognized by the Hematology DSG and are considered within the section describing the DSG Consensus Process.

The study comparing fludarabine with CVP (3) in previously untreated patients was given proportionately less weight. The study results are thus far available in abstract form, have not addressed overall survival, show a difference in median progression-free survival of a relatively small magnitude (494 days vs. 396 days; p not given), and describe more hematologic toxicity in patients receiving fludarabine. In the absence of survival and more complete toxicity data, the magnitude of the progression-free survival difference was considered to be of questionable clinical importance. This trial does, however, demonstrate that fludarabine is an active agent for patients with low grade lymphoma, a finding that contributed to how this drug was regarded when considering options in previously treated patients.
Four other trials conducted in previously untreated patients did not contribute to the DSG conclusions and recommendations. The trials comparing fludarabine with FI (5) and FND with ATT (25) did not include standard control arms and showed no difference in outcomes that would lead to the consideration of new treatment policies. The trials comparing FM with CHEP (4) and CHOP (26) did not report progression-free or overall survival, and/or did not have sufficient follow-up of randomized patients, and were thus considered too preliminary to contribute to recommendations.

**Previously Treated Patients with Low Grade Lymphoma**

Two randomized trials testing fludarabine in previously treated patients with follicular and other low grade lymphoma were identified (6,27). One of these compared fludarabine to a well-described standard therapy in a sufficient number of patients to assess progression-free survival and toxicity and to estimate overall survival (6).

The trial comparing fludarabine with CVP in previously treated patients (6) demonstrated superior progression-free and treatment-free survival in patients receiving fludarabine. No survival difference was detected. A quality-of-life assessment detected superior social function with no differences in other quality-of-life domains (11). These results were considered to be sufficient to recommend fludarabine as an acceptable treatment option for these patients. More complete reporting of results in article form, including a description of the baseline features of the patients, may allow for a better assessment of the time point at which fludarabine should be considered the preferred treatment option.

The trial comparing fludarabine with cladribine (27) did not contribute to the DSG conclusions and recommendations as it did not include a standard control arm.

**Waldenstrom’s Macroglobulinemia**

One randomized trial assessing fludarabine in patients with Waldenstrom’s Macroglobulinemia was identified that compared fludarabine with CAP in previously treated patients (7). The report of this trial demonstrates that fludarabine is an active agent in this disease. Although data are preliminary, fludarabine is associated with a superior response rate, at least comparable outcomes when assessing disease control, and reduced toxicity. These parameters may result in a superior quality of life in patients receiving fludarabine as reported in the preliminary, abstract report assessing quality of life using a Q-TWiST analysis (28). Fludarabine was, therefore, considered an acceptable treatment option in patients previously treated with alkylator-based therapy who have relapsed or refractory disease.

**Economic Evaluations**

The economic evaluations were considered to be preliminary and of a hypothesis-generating nature. These reports did not explicitly indicate the payer perspective of the analyses, did not adequately describe the process used to ensure that the competing treatment options were provided to similar patient groups, and did not include an explicit statement regarding which direct and indirect costs were measured. They appeared to be heavily weighted by the drug acquisition charges rather than by measuring costs. Treatment efficacy outcomes were either assumed to be equivalent or were not considered. Based on these limitations, these data were considered to be insufficient to contribute to conclusions and recommendations.

**VI. ONGOING TRIALS**

The Hematology DSG is aware of the following ongoing trial. The progress of this trial will be monitored and the reported results will be reviewed when available:

**Protocol ID(s) | Title and details of trial**
VII. DISEASE SITE GROUP CONSENSUS PROCESS

The Hematology DSG considered differences in survival and quality of life to be important outcomes upon which treatment recommendations could be based. The DSG also discussed the use of surrogate outcomes, such as response rate and progression-free and treatment-free survivals as proxies for overall survival and quality of life. As improved, progression-free survival may be a desirable outcome for some patients and may translate into improved quality of life; it was considered to be a potentially useful outcome for determining a treatment recommendation. Treatment-free survival may also be a reasonable proxy measure for quality of life as it is assumed that disease progression necessitating therapy would be associated with clinically important symptoms, and deferring any treatment-related toxicity would be valued. However, there may be a bias in measuring this outcome, as none of the randomized trials described were blinded for treatment allocation. Knowing that patients were previously unexposed to fludarabine could favour the re-initiation of fludarabine therapy in patients previously allocated to standard therapy. Treatment-free survival was, therefore, considered in conjunction with progression-free survival in making recommendations. Response rate was felt to be an inadequate surrogate marker upon which to base a treatment recommendation and an outcome more appropriately used in trials reporting results of preliminary new drug testing. Response rate has been included in this report to assist in interpreting progression-free survival when this latter outcome has been reported only in those patients demonstrating a response.

In considering patients with previously untreated low grade lymphoma, the DSG gave greatest weight to the trial comparing fludarabine with CHVP-IFN (2). As this trial showed a difference in all efficacy outcomes, including survival, in favour of the CHVP-IFN group, it was concluded that there was insufficient evidence to support using fludarabine as initial therapy. The DSG recognized that CHVP-IFN is not considered a standard treatment in Ontario. It is generally believed that CHVP and CHOP result in similar outcomes. Furthermore, other than for the potential that more rapid responses are seen in some patients treated with CHOP, it is generally believed that CHOP and CVP produce similar outcomes. With respect to the addition of IFN to chemotherapy, the DSG is aware of the uncertainty of the role of this agent and is in the process of completing a guideline assessing IFN in patients with follicular and other low grade lymphomas. As a result, the DSG concluded that CHVP-IFN may be comparable to the standard regimens (CVP and CHOP) used in Ontario for such patients. The DSG acknowledges the potential risks of drawing these conclusions. The possibility that the risk criteria used in this study (2) may lead to the inclusion of patients with occult transformed lymphoma is also recognized. Such patients may have superior outcomes with CHVP-IFN due to treatment that includes doxorubicin. Separate studies are needed to compare fludarabine with a standard therapy in lower risk patients.

In patients with previously treated low grade lymphoma, the one randomized trial in which fludarabine was compared with a standard option (CVP) demonstrated superior progression-free and treatment-free survival and improvement in one-quality-of life domain (social function) in patients receiving fludarabine; no difference in survival was detected (6). These data were considered sufficient to warrant a recommendation supporting the use of fludarabine as an acceptable treatment option for these patients.
The trial comparing fludarabine with CAP in patients with previously treated Waldenstrom’s Macroglobulinemia showed that fludarabine was associated with superior responses, progression-free survival in responding patients and treatment-free survival in all patients, both with reduced toxicity (7). Although each of these individual outcomes would be considered as having limitations in leading to a recommendation, the sum of these findings, along with the preliminary suggestion of superior quality of life as assessed by a Q-TWiST analysis (28), resulted in the conclusion that fludarabine was an acceptable treatment option.

Finally, the DSG recognizes that the role of monoclonal antibody therapies, such as rituximab, will need to be included in any subsequent determinations of the sequence of therapies for these patients.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence described above, the Hematology DSG drafted the following recommendations:

Target Population

These recommendations apply to adult patients with stage III-IV follicular and other low grade lymphoma or Waldenstrom’s Macroglobulinemia who require therapy. Patients who require initial therapy, or have been previously treated, were considered.

Draft Recommendations

Previously Untreated Patients with Stage III–IV Low Grade Lymphoma

- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; or cyclophosphamide, doxorubicin, vincristine, and prednisone should be considered as first-line therapy, with the choice of treatment determined by patient preferences and clinical judgement. Choice of treatment should take into account factors such as route of administration, risk of infection and outcomes of interest.

Previously Treated Patients with Stage III–IV Low Grade Lymphoma

- Fludarabine is an acceptable option for patients requiring treatment following disease progression after first-line therapy. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone; or rituximab may be appropriate alternatives. Choice of treatment should be determined by patient preferences, clinical judgement, and drug availability and should take into account factors such as the route of administration, the risk of infection and outcomes of interest.

Patients with Waldenstrom’s Macroglobulinemia

- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients.
- Fludarabine is an acceptable option for patients previously treated with alkylator–based therapy who have relapsed or refractory disease.

Qualifying Statements

- Although the incidence of serious infections has been shown to be similar between patients treated with fludarabine and the combination of cyclophosphamide, vincristine, and prednisone, fludarabine significantly depresses T-cell mediated immunity. Prophylaxis against pneumocystis carinii pneumonia with cotrimoxazole should be considered.
- Autoimmune hemolytic anemia, a condition associated with lymphoma, may be exacerbated or precipitated by fludarabine and is considered by the manufacturer as a contraindication to the use of this drug.
The Canadian Blood Services and the British Committee for Standards in Hematology Blood Transfusion Task Force recommend that patients receiving, or who have previously received, fludarabine should receive gamma-irradiated blood products because of the risk of transfusion-related graft-versus-host disease.

Standard therapy with fludarabine consists of 25 mg/m² per day given intravenously for five consecutive days, for a total of six cycles, 28 days apart, or two cycles beyond maximum response.

Related Guidelines
- Practice Guidelines Initiative’s Practice Guideline Report #6-1: Fludarabine in Intermediate- and High-risk Chronic Lymphocytic Leukemia
- Evidence Summary Report #6-8: Rituximab in Lymphoma.

Practitioner Feedback
Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods
Practitioner feedback was obtained through a mailed survey of 178 clinicians (100 medical oncologists and 78 hematologists) in Ontario. The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (second mailing of the complete package). The Hematology DSG reviewed the results of this survey.

Results
Of the 178 surveys sent, seven were excluded due to retirement or leaves, and 87 (51%) were returned. Fifty-three of these respondents (61%) indicated that the practice-guideline-in-progress report was relevant to their clinical practice, and three additional respondents did not complete this question; 56 clinicians completed the survey. Key results of the practitioner feedback survey are summarized in Table 3.
Table 3. Practitioner responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
<th>Strongly agree or agree</th>
<th>Neither agree nor disagree</th>
<th>Strongly disagree or disagree</th>
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<tr>
<td>The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>54 (96)</td>
<td>2 (4)</td>
<td>0</td>
<td></td>
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<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>53 (95)</td>
<td>3 (5)</td>
<td>0</td>
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<tr>
<td>The literature search is relevant and complete.</td>
<td>53 (95)</td>
<td>3 (5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>54 (96)</td>
<td>0</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>55 (98)</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>51 (91)</td>
<td>3 (5)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>48 (87)</td>
<td>6 (11)</td>
<td>1 (2)</td>
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If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?

<table>
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<th>Unsure</th>
<th>Not at all likely or unlikely</th>
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<td></td>
<td>47 (89%)</td>
<td>3 (5)</td>
<td>3 (6)</td>
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Summary of Written Comments

Nineteen respondents (34%) provided written comments regarding the content of the practice-guideline-in-progress report; seven of these indicated support for specific aspects of the report. Twelve other comments included:

1. Two physicians expressed concern regarding the appropriateness of including CHOP as an acceptable first-line treatment option; one other physician indicated that CHVP-IFN should be the treatment of choice.

2. Three physicians indicated that the recommendations are too restrictive for untreated patients and that, based on the results of phase II trials (of fludarabine alone or in combination with other agents) in previously untreated patients, phase III trials in previously treated patients, and phase III trials in patients with chronic lymphocytic leukemia, fludarabine could be recommended as a treatment option for previously untreated patients. One of these respondents noted that the recommendations vary from those used in other parts of Canada.

   However, in addition to the seven comments of support, one other respondent indicated that the recommendation for use in previously untreated patients was not worded strongly enough, and suggested the recommendation should “discourage” the use of fludarabine in these patients.

3. Four respondents expressed concern regarding methodologic issues, including the use of abstracts, limiting the data reviewed to randomized trials, and basing recommendations on a small number of trials assessing a limited number of patients (e.g., Waldenstrom’s Macroglobulinemia).

4. One respondent questioned whether the use of fludarabine might be associated with an improved ability to subsequently harvest autologous stem cells for transplantation.

Modifications/Actions

1. With respect to alternative options for first-line therapy, the DSG recognizes the importance and complexity of this topic but did not intend to create evidence-based recommendations for these alternatives. The DSG agrees that there are circumstances for which first-line use of an anthracycline-containing regimen would be inappropriate but is also aware of circumstances for which this treatment would be reasonable.

2. With respect to the use of phase II data, and of phase III data involving other patient groups, the DSG considered these studies to have interpretive limitations posed by the trial designs. The DSG concluded that recommendations should be based on the results of randomized
trials assessing patients with follicular and other low grade lymphomas. This difference in guideline methodology may account for the variation in resulting recommendations between geographic regions.

3. The DSG recognizes that results from abstracts must be interpreted with caution as the information provided is incomplete and precludes the full assessment of the quality aspects of the study. Abstracts were, therefore, given less weight than published papers in forming recommendations. However, systematic reviews ideally capture the results of all published and unpublished trials to most thoroughly evaluate a topic, including the consideration of publication biases.

4. The DSG did not feel sufficient data were available to comment on the subsequent ability to harvest autologous stem cells.

Based on the above considerations, there were no changes to the draft recommendations.

IX. PRACTICE GUIDELINE
This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Hematology DSG and the Practice Guidelines Coordinating Committee.

Target Population
These recommendations apply to adult patients with stage III-IV follicular and other low grade lymphoma or Waldenstrom’s Macroglobulinemia who require therapy. Patients who require initial therapy, or who have been previously treated, were considered.

Recommendations
Previously Untreated Patients with Stage III–IV Low Grade Lymphoma
- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; or cyclophosphamide, doxorubicin, vincristine, and prednisone should be considered as first-line therapy, with the choice of treatment determined by patient preferences and clinical judgement. Choice of treatment should take into account factors such as route of administration, risk of infection and outcomes of interest.

Previously Treated Patients with Stage III–IV Low Grade Lymphoma
- Fludarabine is an acceptable option for patients requiring treatment following disease progression after first-line therapy. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone; or rituximab may be appropriate alternatives. Choice of treatment should be determined by patient preferences, clinical judgement, and drug availability and should take into account factors such as the route of administration, the risk of infection and outcomes of interest.

Patients with Waldenstrom’s Macroglobulinemia
- There is insufficient evidence to support the use of fludarabine as initial therapy in these patients.
- Fludarabine is an acceptable option for patients previously treated with alkylator-based therapy who have relapsed or refractory disease.

Qualifying Statements
- Although the incidence of serious infections has been shown to be similar between patients treated with fludarabine and the combination of cyclophosphamide, vincristine, and prednisone, fludarabine significantly depresses T-cell mediated immunity. Prophylaxis against pneumocystis carinii pneumonia with cotrimoxazole should be considered.
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Standard therapy with fludarabine consists of 25 mg/m² per day given intravenously for five consecutive days, for a total of six cycles, 28 days apart, or two cycles beyond maximum response.

Related Guidelines
The Practice Guidelines Initiative's:
- Evidence Summary Report #6-8: Rituximab in Lymphoma.

X. ACKNOWLEDGMENTS
The Hematology Disease Site Group would like to thank Drs. J. MacEachern, I. Chin-Yee, K. Imrie, and R. Meyer and Ms. R. Esmail and Ms. J. Makarski for taking the lead in drafting and revising this practice guideline report.

For a complete list of the Hematology Disease Site Group members, please visit the Cancer Care Ontario Web site at http://www.cancercare.on.ca/.
REFERENCES


Treatment with Fludarabine for Patients with Follicular and other Low Grade Non-Hodgkin’s Lymphoma and Waldenstrom’s Macroglobulinemia

Guideline Review Summary


Review Date: March 27, 2013

The 2001 guideline recommendations

REQUIRE UPDATE

This means that the recommendations require additional evidence but are relevant for decision making.

OVERVIEW
Evidence-based Series History

This guidance document was originally released by Cancer Care Ontario’s Program in Evidence-based Care in 2001. In December 2012, the PEBC guideline update strategy was applied and the new document to be updated released in August 2013. The recommendations and the systematic review in this version are the same as June 2001 version.

Update Strategy

Using the Document Review Tool, the PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS
Questions Considered

What are the relative efficacy and other benefits of fludarabine compared with alternative options when treating patients with advanced-stage follicular and other low grade lymphoma and Waldenstrom’s Macroglobulinemia? What are the toxicities of fludarabine? Outcomes of interest include overall survival, progression-free survival, and quality of life.
Literature Search and New Evidence
The new search (Jan 2000 to Jan 1, 2013) yielded 36 relevant new publications representing 22 randomized control trials, 2 Systematic reviews, 6 Existing Guidelines and 6 ongoing clinical trials. Brief results of these publications are shown in the Document Review Tool at the end of this report.

*It was decided that economic reviews are not part of the evidence base required for a treatment guideline and so were not included.*

Impact on Guidelines and Its Recommendations
The new data supports existing recommendations. Hence, the Systemic Treatment DSG (pending approval) ENDORSED the 2004 recommendations on Liposomal Anthracyclines in the Management of Patients with HIV-positive Kaposi’s Sarcoma.
## Document Review Tool

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<th>Number and title of document under review</th>
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<td>Dr. Janet MacEachern</td>
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<td>Research Coordinator</td>
<td>Robert Mackenzie</td>
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<td>Date Assessed</td>
<td>Jan. 2013</td>
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<td>Approval Date and Review Outcome (once completed)</td>
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**Original Question(s):**

1. What are the relative efficacy and other benefits of fludarabine compared with alternative options when treating patients with advanced-stage follicular and other low grade lymphoma and Waldenstrom’s Macroglobulinemia? Outcomes of interest include overall survival, progression-free survival, quality of life.
2. What are the toxicities of fludarabine?

**Target Population:**
These recommendations apply to adult patients with stage III-IV follicular and other low grade lymphoma or Waldenstrom’s Macroglobulinemia who require therapy. Patients who require initial therapy, or who have been previously treated, are considered.

**Study Selection Criteria:**

**Inclusion Criteria**

Articles were selected for inclusion in this systematic review of the evidence if they were one of the following:

1. Randomized controlled trials comparing fludarabine either as monotherapy or in combination with other treatment alternatives in patients with low grade lymphoma or Waldenstrom’s Macroglobulinemia. Primary outcomes of interest included survival, progression-free survival, or quality of life.
2. Reports of fludarabine-related toxicity in patients with low grade lymphoma or Waldenstrom’s Macroglobulinemia.
**Exclusion Criteria**

1. Trials of less than 10 patients (but individual case reports of toxicity were included).
2. Trials including fludarabine as part of a high-dose chemotherapy and/or transplant protocol.

**Search Details:**
- January 2000 to December 31, 2012 (Medline and Embase, ASCO Abstract, ASH Meeting abstract, and Clinicaltrials.gov)

**Brief Summary/Discussion of New Evidence:**
Of 618 total hits from Medline, Embase, ASCO, ASH, and Cochrane Library 22 RCT's (abstracts included), 2 Systematic reviews, 6 Existing guidelines, and 6 on-going clinical trials were identified as relevant sources of information for updating of this guideline.

**Treatment Acronyms**

<table>
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<tr>
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<tr>
<td>FLU</td>
<td>Fludurabine</td>
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<tr>
<td>ID</td>
<td>Idarubicin</td>
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<td>FMD</td>
<td>Fludarabine, Mitoxantrone, Dexamethasone</td>
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<tr>
<td>CMD</td>
<td>Chlorambucil Mitoxantrone and Dexamethasone</td>
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<td>FC</td>
<td>Fludarabine, Cyclophosphamide</td>
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<td>FCR</td>
<td>Fludarabine, Cyclophosphamide, Rituximab</td>
</tr>
<tr>
<td>CHOP</td>
<td>Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone</td>
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<tr>
<td>R-CHOP</td>
<td>Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone</td>
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<td>FCM</td>
<td>Fludarabine, Cyclophosphamide, Mitoxantrone</td>
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<td>R-FCM</td>
<td>Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone</td>
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<td>CVP</td>
<td>Cyclophosphamide, Vincristine, Prednisone</td>
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<tr>
<td>R-CVP</td>
<td>Rituximab, Cyclophosphamide, Vincristine, Prednisone</td>
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| Fludarabine, Mitoxantrone and Dexamethasone (FMD) Vs. Chlorambucil Mitoxantrone and Dexamethasone (CMD) | Results of a prospective randomised trial comparing chlorambucil, mitoxantrone and dexamethasone (CMD) versus fludarabine, mitoxantrone and dexamethasone as primary therapy for advanced stage follicular lymphoma (real grades I-III, stage III/IV). A report from the UK central and southern lymph. | n=400          | PFS, OS  | • HR for OS at 1.48 (95% CI 0.91-2.31, p=0.11)  
• HR for PFS at 1.44 (95% CI 1.08-1.93, p=0.013)  
• Median PFS was 43 months for CMD versus 33 months for FMD | Lush RJ et al. (2009) |
| Intravenous FC/ FCR (iv): Fludarabine (F) 25 mg/m2/d plus cyclophosphamide (C) 250 mg/m2/d (d 1-3), Rituximab (R) 375 mg/m2 (d1) x 4 28-day cycles; Vs. Oral FCR (po): F 30 mg/m2/d plus C 175 mg/m2/d (d 1-3), R 375 mg/m2/d (d1) x 4-6 28-day cycles. Stages III-IV and FLIPI= 3 patients at diagnosis achieving CR1 received R maintenance: R 375 mg/m2 q/3 months x 8 doses. Toxicity was recorded at every cycle and thereafter during follow-up, and classified according to the NCI Common | Low-intensity fludarabine, cyclophosphamide, rituximab (FCR) as front-line treatment for follicular lymphoma. Efficacy and toxicity profile of the oral versus intravenous administration | n=96   | Toxicity, OS | • 53/86 pts presented neutropenia grade 3-4: 21 (56.7%) and 32 (85.3%) in FCRiv and FCRpo respectively (p=0.02)  
• Grade 3-4 thrombocytopenia occurred in 7 FCRiv and 1 FCRpo pts (p=0.03)  
• Anemia grade 3-4 in 5 FCRiv and 1 FCRpo (p=0.02)  
• With a MFU: 25.7 m (0.3-119.4), overall survival (OS) was 95.4% (IC 95% = 9.3-100%), mean OS= 114.6 m (IC95% 109.3-119.9) and event-free survival (EFS) - considering progression, relapse or death - was 85.3% (IC95% 73.7-96.8%), mean EFS= 106.2 m (IC95% 96.6-115.8 m. No significant differences were found between oral and iv | Marin-Nebula A., et al. (2009) |
<table>
<thead>
<tr>
<th>Interventions</th>
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<th>Brief results</th>
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<tr>
<th>Intravenous FC Vs. FCR</th>
<th>Efficacy and safety of low-intensity oral and intravenous fludarabine-cyclophosphamide with and without Rituximab for first-line treatment of follicular lymphoma</th>
<th>N=81 Follicular lymphoma (WHO histological grades 1-2) patients (pts.) aged &gt;=18, previously untreated, WHO-PS&lt;=2, &lt;=2-fold renal and hepatic function values</th>
<th>OS, EFS, Toxicity</th>
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<tr>
<td>Fludarabine (F) 25 mg/m²/d plus Cyclophosphamide (C) 250 mg/m²/d (d 1-3), Rituximab (R) 375 mg/m²/d (d1) x 4 28-day cycles;</td>
<td>28-day cycles;</td>
<td>Neutropenia was the most limiting AE</td>
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<td>Oral FCR (pop): F 30 mg/m²/d plus C 175 mg/m²/(d1) x 4-6 28-day cycles; R maintenance (advanced stage achieving CR): R 375 mg/m²/d (d1) x 4 28-day cycles;</td>
<td></td>
<td>25 neutropenia 3-4 episodes: 15 (55.5%) and 8 (17.4%) in Crib and FCR-pop respectively (p&lt;0.001);</td>
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<td>grade 3-4 infection rate: 13 (46.4%) and 7 (15.2%) in Crib and Crop, respectively (p&lt;0.001), causing death in 2/28 Crib pts.</td>
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<td>Grade 3-4 thrombocytopenia occurred in 3 Crib and 2 Crop pts.</td>
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<td>anemia 3-4 in 2 Crib and 1 Crop,</td>
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<td>1 case of liver toxicity (Crib).</td>
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<td>40 pts. received R-Maintenance: Crib: 20/27 (74%), Crop: 20/46,</td>
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<td>Withdrawal of R-maintenance due to neutropenia and infections: 9 (45%) Crib and 3 (15%) Crop.</td>
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<td>3 pts. relapsed with a M TTP: 12 m (9-14); and 3 pts. died (2 infections, 1 progression). overall survival (OS) was 94.6% (IC at 95%: 88.5 to 100%),</td>
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<td>(EFS) was 90%, no significant differences between oral and iv FCR</td>
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<td>Transformation to aggressive NHL occurred in 2 pts., no cases myelodysplasia</td>
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| Cases were randomly allocated to FM (fludarabine plus mitoxantrone) **Vs.** CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). | Fludarabine plus mitoxantrone with and without rituximab versus CHOP with and without rituximab as front-line treatment for patients with follicular lymphoma | N=140 Confirmed histologic diagnosis according to the Revised European American classification 34 of FL grade 1 and 2 CD20 positive; a positive PCR analysis on bone marrow (BM) and peripheral blood (PB); stage II to IV according to the Ann Arbor staging system; 35 an Eastern Cooperative Oncology Group 36 performance status of 0, 1, or 2; HIV negativity as tested at diagnosis; and normal renal, pulmonary and hepatic functions. | Response rate, PFS, OS | - Estimated global OS at 3 years is 94%, with a global PFS of 63%  
- Estimated 3-year RFS rate was 71% among the 28 patients who achieved combined clinical and molecular response after FM chemotherapy  
- 3-year RFS was 58% with four patients (30%) experiencing disease relapse among the 13 who had CR after CHOP (P=.20).  
- The estimated 3-year RFS rates of patients who obtained CR or only CR after the entire sequential treatment program (ie, FM/CHOP with or without rituximab) were 66% and 44%, respectively | Zinzani P.L., et al. (2004) |
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<td>Six cycles of rituximab plus fludarabine and cyclophosphamide (R-FC) <strong>Vs.</strong> Six cycles of fludarabine and cyclophosphamide alone (FC)</td>
<td>Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia</td>
<td>N=552 Previously treated CLL. A total of 552 patients with Binet stage A (1%), B (59%), or C (31%) disease</td>
<td>PFS, SAE’s, QOL</td>
<td>• Rituximab significantly improved progression-free survival in patients with previously treated CLL (hazard ratio = 0.65; p &lt; .001; median, 30.6 months for R-FC v 20.6 months for FC). Event-free survival, response rate, complete response rate, duration of response, and time to new CLL treatment or death were also significantly improved. Although the rates of adverse events, grade 3 or 4 events, and serious adverse events were slightly higher in the R-FC arm, R-FC was generally well tolerated, with no new safety findings and no detrimental effect on quality of life</td>
<td>Robak T., et al. (2010)</td>
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<td>FLU group (six monthly cycles of FLU 25 mg/m²/d on days 1 through 5)</td>
<td>Randomized trial of fludarabine versus fludarabine and idarubicin as frontline treatment in patients with indolent or mantle-cell lymphoma</td>
<td>N=199 newly diagnosed stages II to IV indolent or mantle-cell lymphomas</td>
<td>Response rates, toxicity</td>
<td>• No striking differences were observed between the two protocols in terms of overall response or toxicity, which was generally mild. • However, with a median follow-up of 19 months, only 29 patients (62%) who received FLU alone have maintained their initial CR, compared with 32 (84%) of those who received FLU-ID therapy (p = .021).</td>
<td>Zinzani P.L., et al (2000)</td>
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<td>FLU-ID group (six monthly cycles of FLU 25 mg/m²/d on days 1 through 3 and</td>
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<td>idarubicin 12 mg/m² on day 1)</td>
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<td>4 courses of chemotherapy with 25 g/m&lt;sup&gt;2&lt;/sup&gt; fludarabine on days 1 to 3,</td>
<td>The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group</td>
<td>n=147 Follicular lymphoma (FL) and mantle cell lymphoma (MCL)</td>
<td>PFS, OS</td>
<td>• R-FCM arm was significantly superior concerning progression-free survival (PFS; p = .0381) and overall survival (OS; p = .0030). • In FL PFS was significantly longer in the R-FCM arm (p = .0139) whereas in MCL a significantly longer OS was observed (p = .0042). • There were no differences in clinically relevant side effects in both study arms.</td>
<td>Forstpointner et al. (2004)</td>
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<td>200 mg/m&lt;sup&gt;2&lt;/sup&gt; cyclophosphamide on days 1 to 3, and 8 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>mitoxantrone on day 1 (FCM),</td>
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<td>Vs. 4 courses of chemotherapy with 25 g/m&lt;sup&gt;2&lt;/sup&gt; fludarabine on days 1 to 3,</td>
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<td>200 mg/m&lt;sup&gt;2&lt;/sup&gt; cyclophosphamide on days 1 to 3, and 8 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>mitoxantrone on day 1 (FCM), combined with rituximab (375 mg/m&lt;sup&gt;2&lt;/sup&gt;); R-FCM)</td>
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<td>Fludarabine (25 mg/m&lt;sup&gt;2&lt;/sup&gt;/intravenously [IV] daily for 5 days every 4 weeks) Vs. CVP (cyclophosphamide 750 mg/m&lt;sup&gt;2&lt;/sup&gt;/IV on day 1; vincristine, 1.4 mg/m&lt;sup&gt;2&lt;/sup&gt;/IV on day 1; and prednisone, 40 mg/m&lt;sup&gt;2&lt;/sup&gt;/orally on days 1 through 5 every 4 weeks)</td>
<td>Phase III intergroup study of fludarabine phosphate compared with cyclophosphamide, vincristine, and prednisone chemotherapy in newly diagnosed patients with stage III and IV Low-grade malignant non-Hodgkin's lymphoma</td>
<td>n=381 previously untreated, advanced-stage, low-grade (Ig) non-Hodgkin's lymphoma (NHL)</td>
<td>OS, TTP, Toxicity</td>
<td>• There were no statistically significant differences in time to progression (TTP), time to treatment failure (TTF), and overall survival (OS) between treatment groups. • WHO grades 3 and 4 hematologic adverse events were more common in the fludarabine arm</td>
<td>Hagenbeek et al. (2006)</td>
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# ABSTRACTS

## Interventions

| 4 courses of chemotherapy with Fludarabine (25 mg/m²/day days 1–3), Cyclophosphamide (200 mg/m²/day days 1–3) and Mitoxantrone (8 mg/m²/day 1) (FCM) **Vs.** 4 courses of chemotherapy with Fludarabine (25 mg/m²/day days 1–3), Cyclophosphamide (200 mg/m²/day days 1–3) and Mitoxantrone (8 mg/m²/day 1) (FCM) ± Rituximab (375 mg/m²/day 0) | Rituximab maintenance improves progression-free and overall survival rates after combined immunotherapy (R-FCM) in patients with relapsed follicular and mantle cell lymphoma: Final results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG) | N=195 Patients with advanced stage relapsed or refractory FL and mantle cell lymphoma (MCL) were eligible | MPFS | • median PFS after end of induction has not been reached in the R-maintenance arm in contrast to 17 months in patients with no further treatment (p = 0.001). This improvement was seen both in FL (n = 81; p = 0.035) and MCL (n = 47; p = 0.049) | Dreyling M., et al. (2006) |
| Fludarabine containing regimen (FCM) was chosen for salvage therapy **Vs.** Fludarabine containing regimen (FCM) for salvage therapy followed by Rituximab maintenance | Combined immunotherapy (R-FCM) results in superior remission rates and overall survival in recurrent follicular and mantle cell lymphoma: Follow-up of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG) | N=244, 122 (50%) had follicular, 95 (39%) mantle cell and 24 (10%) with other indolent lymphomas | PFS, OS, remission rates | • In 67 randomized patients with follicular lymphoma, progression-free survival (median: 3.9 vs. 1.7 years, p=0.029) and overall survival (74% at 4 years vs. median of 3.8 years, p=0.033) was significantly improved after combined immunotherapy. • 55 patients subsequently designated to the combined study arm (R-FCM) confirmed the superior remission rates (36%/96%), progression-free and overall survival. • Similarly, in 50 randomized MCL patients, R-FCM achieved higher overall survival (median: 2.5 vs 0.9 years, p=0.031). The improved overall survival was | Dreyling M., et al. (2005) |
### Interventions | Abstract Name | Population (n) | Outcomes | Brief results | Ref. |
|----------------|----------------|----------------|----------|--------------|------|
| **R-CVP Vs. R-CHOP** | R-CVP versus R-FM as first-line therapy for advanced-stage follicular lymphoma: Final results of FOLL05 trial from the Fondazione Italiana Linfomi (FIL) | N=504(534-30) Previously untreated patients with advanced Follicular lymphoma | 3 yr OS, PFS, toxicity, 2nd malignancies | - 3-year overall survival rate (OS) was 98%, 95% and 93% for R-CVP, R-CHOP and R-FM group, respectively (p=NS).  
- Patients treated with R-FM had a higher rate of g III-IV neutropenia (64% vs 28% R-CVP, p<0.001; and vs 50% R-CHOP, p=0.015).  
- During follow-up second malignancies were registered as late events in 23 patients (2%, 3% and 8% in R-CVP, R-CHOP and R-FM, respectively) | Federico M., et al. (2012) |
| **Induction CVP (cyclophosphamide, vincristine, prednisone) Vs. CF (cyclophosphamide 1 G/m² d1, fludarabine 20 mg/m² d1-5 every 28 d)** | Cyclophosphamide and fludarabine (CF) in advanced indolent lymphoma: Results from the ECOG/CALGB intergroup E1496 trial | N=234 Due to early deaths the CF arm was closed | OS, PFS | - Toxic deaths occurred in 8 (7%) CF pts during induction and 4 additional deaths (1 OBS, 3 MR) occurred among the 69 (6%) CF pts randomized to MR or OBS  
- Four-yr PFS for CF vs. CVP was 49% vs 45% (p=0.19) and OS was 66% vs. 81% (p=0.12)  
- Maintenance therapy had no impact on 2 yr PFS for the 67 evaluable randomized CF pts, which was 74% for MR vs. 73% for OBS (p=0.19).  
- In contrast, 2 yr PFS was 73% for MR and 42% for OBS in randomized CVP pts (p=0.004) | Hochster H.S., et al. (2007) |
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<tr>
<td>After completing induction therapy, patients were randomized to receive either Zevalin (250 mg/m² rituximab on day -7 and on day 0 followed on day 0 by Zevalin 0.4 mCi/kg; maximal dose: 32 mCi) <strong>Vs.</strong> no further treatment</td>
<td>^Y-Ibritumomab Tiuxetan (Zevalin®) Consolidation of First Remission in Advanced Stage Follicular Non-Hodgkin's Lymphoma: First Results of the International Randomized Phase 3 First-Line Indolent Trial (FIT) in 414 Patients.</td>
<td>n=414</td>
<td>PFS, toxicity</td>
<td>• median PFS increased from 13.5 (controls) to 37 mo (Zevalin; p&lt;0.0001; HR 0.463). For patient subgroups in PR or CR after induction, median PFS was 6.3 vs 29.7 mo (p&lt;0.0001; HR 0.304) and 29.9 vs 54.6 mo (p=0.01; HR 0.609), respectively. • Toxicity was primarily hematologic:</td>
<td>Hagenbeek A., et al. (2007)</td>
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<td>CMD (chlorambucil 10mgs po, od, days 1–10, mitoxantrone 12mgs/m² IV, day 1 and dexamethasone 20mgs po, od, days 1–5) <strong>Vs.</strong> FMD (fludarabine 25mgs/m², IV days 1–3, with M and D as for CMD)</td>
<td>A Prospective, Randomised Trial of Chlorambucil, Mitoxantrone and Dexamethasone (CMD) Versus Fludarabine, Mitoxantrone and Dexamethasone (FMD) for Advanced Follicular Lymphoma (Real Grades I-III, Stages III/IV)</td>
<td>n=400 de novo and relapsed/refractor y follicle centre cell lymphoma (FCCL)</td>
<td>PFS, OS</td>
<td>• hazard ratios were in favour of CMD, for OS at 1.65 (95%CI 0.97–2.8, p=0.063) and for PFS at 1.61 (95%CI 1.2–2.17; p=0.0018) • The equivalent dose intensity, toxicities and RRs of the two arms indicate that the statistically significant superior PFS for CMD was not due to undertreatment in the FMD arm.</td>
<td>Haynes A., et al. (2006)</td>
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<td>8 x R-CHOP-21 (day 1: rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m², max 2 mg and day 1–5 prednisone 100 mg) <strong>Vs.</strong> 6 x R-FC-28 (rituximab 375 mg/m² day 1, fludarabine 30 mg/m² + cyclophosphamide 250 mg/m², both iv day 1–3).</td>
<td>R-CHOP Versus R-FC Followed by Maintenance with Rituximab Versus Interferon-Alfa: Outcome of the First Randomized Trial for Elderly Patients with Mantle Cell Lymphoma</td>
<td>n=560 stage II-IV MCL &gt;60 yrs not eligible for high-dose therapy</td>
<td>OS</td>
<td>• median OS was significantly inferior after R-FC (40 vs 64 months; p=0.0072) • Overall survival did not differ between both maintenance arms (p=0.17)</td>
<td>Kluin-Nelemans J.C., et al (2011)</td>
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every 2 months or interferon-alfa (IFN; regular IFN weekly 3x3 MIU or pegylated IFN 1x1 μg/kg), both given until progression.

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| Oral CBL at a dose of 8 mg/m² for 10 days every 28 days to a maximum of 12 cycles | International Phase III Study of Chlorambucil Versus Fludarabine As Initial Therapy for Waldenstrom’s Macroglobulinemia and Related Disorders: Results in 414 Patients on Behalf of FCG CLL/ WM, GOELAMS, GELA, NCRI, ALLG | n=405 previously untreated WM MZL and LPL | PFS, DFS OS | • PFS 36.3m vs 27.1 m (p=0.01) and DFS 38.3m vs 19.9m (p=0.0006)  
• Overall survival rate at 5 years was 61.4% [52.9;71.3] in CBL arm and 70.3% [62.7-78.8] in F arm (p=0.04) | Leblond V., et al. (2011) |
| Up to 8 cycles of oral FC (Fludarabine 40mg/m² and Cyclophosphamide 250mg/m² both daily x 3) given every 4 weeks vs. Up to 8 cycles of oral FC (Fludarabine 40mg/m² and Cyclophosphamide 250mg/m² both daily x 3) given every 4 weeks And Rituximab 375mg/m² on day 1 | The Addition of Rituximab to Fludarabine and Cyclophosphamide (FC) Improves Overall Survival in Newly Diagnosed Mantle Cell Lymphoma (MCL): Results of the Randomised UK National Cancer Research Institute (NCRI) Trial | n=370 Newly diagnosed patients with MCL | PFS, OS | • median follow up of 38.8 months the median PFS is 30.6 months in the FCR arm and 16.1 months in the FC arm. The median OS is 45.7 months for FCR and 37 months for FC  
• Patients in the FCR arm had longer progression free and overall survival with HRs of 0.56 (95% CI: 0.43–0.73, p < 0.001) and 0.72 (95% CI: 0.54–0.97, p = 0.03) respectively | Rule S., et al. (2011) |
| Rituximab 375 mg/m² (day 1) plus bendamustine 90 mg/m² (days 1+2) vs. Rituximab 375 mg/m² (day 1) plus fludarabine 25 mg/m² (days 1–3) q 28 days for a maximum of 6 cycles. Prophylactic use of antibiotics or granulocyte-colony stimulating factor (G-CSF) was not generally recommended; however in cases of severe granulocytopenia, G-CSF use was permitted. The protocol was amended in 2006 to allow rituximab maintenance therapy (rituximab 375 mg/m² q 28 days for a maximum of 6 cycles) | Bendamustine Plus Rituximab Versus Fludarabine Plus Rituximab In Patients with Relapsed Follicular, Indolent and Mantle Cell Lymphomas - Final Results of the Randomized Phase III Study NHL 2-2003 on Behalf of the StiL (Study Group Indolent Lymphomas, Germany) | n=219 pts with relapsed FL, indolent or MCL in need of treatment | PFS | • Median PFS was significantly prolonged with B-R compared with F-R (30 vs 11 months; hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.34–0.67; p<0.0001) | Rummel M.J., et al. (2010) |
mg/m² q 3 months for up to 2 years) in both arms, following regulatory approvals in this setting.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Abstract Name</th>
<th>Population (n)</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 BACOP treatments followed by 4 cycles of FND.</td>
<td>Anthracycline-Fludarabine Containing Regimens with or without Rituximab in the Treatment of Advanced Follicular Lymphoma Patients</td>
<td>n=94</td>
<td>FFS, OS</td>
<td>• BACOP/FND. Response rates by intent to treat analysis were: ORR 90%, CR 62%. No differences were observed in FFS and OS between the 2 arms of maintenance.</td>
<td>Sacchi S., et al. (2008)</td>
</tr>
<tr>
<td>4 courses of R-FND (standard doses of Rituximab, Fludarabine, Mitoxantrone, Dexamethasone) every 28 days followed by four weekly Rituximab infusions as consolidation; responding (Complete Response, CR + CRu + Partial Response, PR) patients were randomized between a short Rituximab maintenance with a single dose every two months for a total of four doses (Arm A) vs. observation (Arm B)</td>
<td>Brief Chemoimmunotherapy R-FND with Rituximab Consolidation Followed by Randomization Between Rituximab Maintenance Vs. Observation As First Line Treatment in Elderly Patients with Advanced Follicular Lymphoma (FL): Final Results of a Prospective Randomized Trial by Italian Lymphoma Foundation (FIL)</td>
<td>N=234 advanced stage II 14%, stage III 21% and stage IV 65%</td>
<td>PFS, OS</td>
<td>• R consolidation. With a median follow-up of 33 months, two-years Overall Survival and Progression Free Survival (PFS) were 93% (95% CI 92%–97%) and 77% (95% CI 71%–93%), respectively.  • Two-years PFS according to maintenance/observation phase was: 80% vs 68%</td>
<td>Vitolo U., et al. (2011)</td>
</tr>
<tr>
<td>6 monthly cycles of fludarabine plus rituximab (FR) followed 2 months later by 4 weekly doses of rituximab (concurrent arm) vs. 6 monthly cycles of single agent fludarabine followed by rituximab consolidation using 4 weekly doses (sequential arm)</td>
<td>Treatment with Fludarabine and Rituximab Produces Extended Overall Survival (OS) and Progression-Free Survival (PFS) in Chronic Lymphocytic Leukemia (CLL) without Increased Risk of Second Malignancy: Long-Term Follow up of CALGB Study 9712</td>
<td>N=104 Previously untreated CLL</td>
<td>PFS, OS</td>
<td>• Median OS was 85 months (95% CI: 71-95)  • Median PFS was 37 months (95% CI: 27-45)  • estimated median OS and PFS for the concurrent group- 84 months (95% CI: 57-100) and 32 months (95% CI: 23-55)  • Median OS and PFS for sequential group were 91 months (95% CI: 71-110) and 40 months (95% CI: 23-50), respectively  • Patients with del(17p13.1)/del(11q 22.3)(18 ts) and unmutated IgVH(43) have an inferior OS (p=0.01 and p=0.04,</td>
<td>Woyach J.A., et al. (2009)</td>
</tr>
</tbody>
</table>
respectively) and PFS (p=0.03 and p=0.04, respectively) compared to those without these abnormalities.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Abstract Name</th>
<th>Population (n)</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>Ref.</th>
</tr>
</thead>
</table>
| 6 cycles of rituximab plus fludarabine and cyclophosphamide (R-FC) **Vs.** 6 cycles of fludarabine and cyclophosphamide alone (FC) | Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia | n=552 previously treated CLL. A total of 552 patients with Binet stage A (1%), B (59%), or C (31%) disease | PFS, EFS | • rituximab significantly improved progression-free survival in patients with previously treated CLL (hazard ratio = 0.65; p < .001; median, 30.6 months for R-FC v 20.6 months for FC).  
• Event-free survival, response rate, complete response rate, duration of response, and time to new CLL treatment or death were also significantly improved. | Robak T. et al (2010) |
## SYSTEMATIC REVIEW &/OR META-ANALYSIS

<table>
<thead>
<tr>
<th>Name of Study</th>
<th>Population (n)</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
</table>
| Improvement of overall and failure-free survival in stage IV follicular lymphoma: 25 years of treatment experience at The University of Texas M.D. Anderson Cancer Center | n=580          | OS, FFS, and survival after first relapse | ▪ Improvements in 5-year OS (from 64% to 95%) and FFS (from 29% to 60%) indicate steady progress, perhaps partly due to more effective salvage therapies, but the FFS data also indicate improved front-line therapies; these observations held true after controlling for differences in prognostic factors among the cohorts.  
▪ The FLIPI model adds rigor to and facilitates comparisons among the different cohorts.  
▪ An unexpected finding in this study was a trend toward an apparent FFS plateau. | Liu Q., et al.  
(2006) |
| Treatment regimens included: cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin (CHOP-Bleo); CHOP-Bleo followed by interferon alfa (IFN-alpha); a rotation of three regimens (alternating triple therapy), followed by IFN-alpha; fludarabine, mitoxantrone, dexamethasone (FND) followed by IFN-alpha; and FND plus delayed versus concurrent rituximab followed by IFN-alpha. | n=1943         | OS, ORR, TTFC, EFS, Toxicity | ▪ Patients treated with R-chemo  
▪ HR for mortality 0.65; 95% CI 0.54 to 0.78,  
▪ ORR HR 1.21; 95% CI 1.16 to 1.27,  
▪ disease control HR of disease event 0.62; 95% CI 0.55 to 0.71  
▪ R-chemo improved overall survival in patients with follicular lymphoma (HR for mortality 0.63; 95% CI 0.51 to 0.79) and in patients with mantle cell lymphoma (HR for mortality 0.60; 95% CI 0.37 to 0.98). However, in the latter case, there was heterogeneity among the trials (p=0.07), making the survival benefit less reliable | Shulz H., et al.  
(2007) |
## Existing Guidelines

<table>
<thead>
<tr>
<th>Title</th>
<th>Recommendations</th>
<th>Source</th>
<th>Pub. Date</th>
</tr>
</thead>
</table>
| Non-Hodgkin’s lymphomas: Clinical practice guidelines in oncology | **First Line Therapy**  
- Rituximab based. Regimens include: Rituximab, Bendamustine + rituximab, RCHOP, RCVP.  
- **Elderly or Infirm**  
  - Radioimmunotherapy, Rituximab, single agent alkylators (Chlorambucil or cyclophosphamide) ± Rituximab  
- **Second line and Subsequent**  
  - Chemoimmunotherapy (as above)  
  - FCMR  
  - Fludarabine ± Rituximab  
  - Lenalidomide ± Rituximab  
  - Radioimmunotherapy  
  - Rituximab  
  - RFND | Zelenetz A.D., et al., et al. | 2013(v1) |
| Lymphoma | **Follicular Lymphoma**  
- For grades 1.2.3a follicular lymphoma who have an indication for therapy, the recommended therapy involves 6-8 cycles of R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) chemotherapy, followed in responding patients by 2 years of maintenance rituximab (375mg/m² 2 IV single dose every 3 months for total of eight doses)  
- Therapeutic recommendations for recurrent follicular lymphoma need to be individualized, and no one recommendation is suitable for all patients  
- Indolent lymphomas should generally be treated similarly to follicular grade 1-2 lymphomas  
**Lymphoplasmacytic Lymphoma (LPL) & Waldenstrom macroglobulinemia (WM)**  
- Plasmapheresis: 1-2 procedures, exchanging 1-1.5 calculated plasma volumes, are advised for the treatment of HVS in WM, followed by chemotherapy to prevent paraprotein re-accumulation. In patients who are drug-resistant, plasmapheresis may be indicated for long-term management. Although there are few studies that consider the role of plasma exchange in the treatment of cryoglobulinemia, there is a clear rationale for its use. The treatment room should be warm and blood warmers used in the cell separator circuit to prevent precipitation during the procedure.  
- Chemotherapy: The most common initial... | Alberta Health Services | 2012 |
Chemotherapy for LPL is R-CVP followed by rituximab maintenance, similar to other indolent B-cell lymphomas. Alkylating agent-based therapy or purine analogues are also reasonable for the initial and subsequent treatment of WM, especially for older patients with significant co-morbid illnesses. There is no consensus on the duration of treatment with cladribine or fludarabine, or on which purine analogue is superior.

- Thalidomide is of potential use in the treatment of patients who have previously received alkylating agents, purine analogues and antibody therapy.
- High-dose therapy supported by autologous SCT has a role in the management of selected patients with WM who have chemosensitive primary induction failure or relapsed disease (preferably first relapse).

Waldenstrom’s macroglobulinemia/lymphoplasmacytic lymphoma, version 2.2013: Featured updates to the NCCN guidelines

- Treatment should be initiated for patients with a diagnosis of WM/LPL only in those who are symptomatic.
- For patients requiring immediate disease control, such as those with symptomatic hyperviscosity, initial plasmapheresis is recommended. After plasmapheresis, treatment should be initiated as soon as possible.
- The primary treatment options include oral alkylators (eg, chlorambucil); nucleoside analogs (cladribine or fludarabine); rituximab as single agent; or rituximab in combination with cyclophosphamide, bortezomib, nucleoside analogues, thalidomide, or bendamustine.
- Exposure to continuous oral alkylator therapy or nucleoside analogs should be avoided if a stem cell transplant is being considered.
- For patients showing a response to primary treatment, the follow-up options could include either observation until the disease progresses or the use of maintenance rituximab therapy.
- Administering the same regimen used for primary treatment is reasonable as second-line or salvage therapy for relapsed disease if a patient achieved a response that lasted for at least 12 months or more; otherwise, use of an alternate single agent or combination is recommended.

Diagnosis and management of Waldenstrom macroglobulinemia: Mayo stratification of macroglobulinemia and risk-adapted therapy (mSMART) guidelines

- Patients with IgM MGUS or smoldering (asymptomatic) Waldenstrom macroglobulinemia (WM) and preserved hematologic function should be observed without initial therapy.
- Patients with symptomatic (WM) and modest hematologic compromise, IgM-related neuropathy requiring treatment, or hemolytic anemia unresponsive to corticosteroids should receive standard doses of rituximab alone without maintenance therapy.
- Patients with (WM) who have severe constitutional symptoms, profound hematologic compromise, bulky
disease, or hyperviscosity should be treated with the DRC regimen. Any patient with symptoms of hyperviscosity should first undergo plasmapheresis.

- Because there is no standard approach to the management of patients with relapsed (WM) these patients should always be considered for participation in clinical trials. Two further issues need to be considered–whether the patient had a durable response to frontline therapy and whether the patient is a candidate for an autologous stem cell transplant.

SEOM clinical guidelines for the treatment of follicular non-Hodgkin's lymphoma.

**Stage I–II disease**
- Radiotherapy with an extended 30–40 Gy field is the preferred treatment option, achieving excellent survival rates and long-term disease control.
- Patients who present with a large tumour burden can be treated with the same frontline chemotherapy used for advanced-stage disease prior to radiotherapy. Observation may be an option only if radiotherapy will cause specific toxicity or in patients with stage I disease without residual lymphoma after excisional biopsy

**Stage III–IV disease**
- Participation in clinical trial should be considered. If decision is to pursue treatment then chemotherapy and Rituximab comination (R-CHOP, R-CVP, R-bendamustin, R-fludurabine) should be considered.

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

**Stage I–II disease**
- In the small proportion of patients with limited non-bulky stages I–II, radiotherapy (involved or extended field, 30 36 Gy) is the preferred treatment having a curative potential. In selected cases a watchful waiting may be discussed to avoid the side effects of radiation
- In patients with large tumor burden or adverse prognostic features, systemic therapy as indicated for advanced stages should be applied and the role of radiation consolidation is not proven

**Stage III–IV disease**
- If complete remission and long PFS are to be achieved, rituximab in combination with chemotherapy [such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), CVP (cyclophosphamide, vincristine and prednisone), purine analog-based schemes: FC (fludarabine and cyclophosphamide) or FM (fludarabine and mitoxantrone) or Bendamustine] should be used. In cases with (histologically or clinically) suspected transformation to aggressive lymphoma, an anthracycline-based regimen should be preferred.
## On-GOING Clinical Trials

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Official title</th>
<th>Status</th>
<th>Protocol ID</th>
<th>Last Updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine plus Rituximab <strong>Vs.</strong> Fludarabine plus Rituximab</td>
<td>Prospective Randomised Multicenter Study for Therapy Optimization of Recurrent, Progressive Low Grade Non-Hodgkin Lymphomas and Mantle Cell Lymphomas</td>
<td>completed</td>
<td>NCT01456351</td>
<td>February 11, 2013</td>
</tr>
<tr>
<td>Cyclphosphamide, fludarabine <strong>Vs.</strong> Cyclphosphamide, vincristine, prednisone</td>
<td>Randomized Phase III Study in Low Grade Lymphoma Comparing Maintenance Anti-CD20 Antibody Versus Observation Following Induction Therapy</td>
<td>completed</td>
<td>NCT00003204</td>
<td>February 26, 2013</td>
</tr>
<tr>
<td>R-CVP repeated every 21 days for up to 8 cycles with response assessment after 4 cycles. Responders (PR/CR) after 8 cycles will receive Rituximab maintenance therapy for 2 years (12 bi-monthly cycles). <strong>Vs.</strong> R-FC repeated every 21 days for 4 cycles. Responders (PR/CR) after 4 cycles will receive 4 further cycles of Rituximab only. Responders after 8 cycles will receive Rituximab maintenance therapy for 2 years (12 bi-monthly cycles).</td>
<td>Purine-Alkylator Combination In Follicular Lymphoma Immuno-Chemotherapy for Older Patients: a Phase III Comparison of First-line R-CVP Versus R-FC</td>
<td>Recruiting</td>
<td>NCT01303887</td>
<td>May 4, 2011</td>
</tr>
<tr>
<td>Study Title</td>
<td>Design</td>
<td>Status</td>
<td>NCT Number</td>
<td>Recruitment Start</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Efficacy of Maintenance Therapy With Rituximab After Induction Chemotherapy (R-CHOP vs. R-FC) for Elderly Patients With mantle cell lymphoma Not Suitable for Autologous Stem Cell Transplantation</td>
<td>Recruiting</td>
<td></td>
<td>NCT00209209</td>
<td>September 6, 2012</td>
</tr>
<tr>
<td>Purine-Alkylator Combination In Follicular Lymphoma Immuno-Chemotherapy for Older Patients: a Phase III Comparison of First-line R-CVP Versus R-FC</td>
<td>Recruiting</td>
<td></td>
<td>NCT01303887</td>
<td>May 4, 2011</td>
</tr>
<tr>
<td>Open-label, Multicenter, Randomized, Comparative, Phase III Study to Evaluate the Efficacy and Safety of FCR vs. FC Alone in Previously Treated Patients With CD20 Positive B-cell CLL</td>
<td>completed</td>
<td></td>
<td>NCT00090051</td>
<td>January 14, 2013</td>
</tr>
</tbody>
</table>

DFS= disease free survival; EFS = event free survival; HR= hazard ratio; N/A= not available; ORR= overall response rate; OS= overall survival; RR= risk ratio;
**Instructions.** These questions are answered by the Clinical Expert assigned by the DSG/GDG. Beginning at question 1 answer the questions in order, following the instructions in the black boxes as you go.

<table>
<thead>
<tr>
<th>1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.No</td>
</tr>
<tr>
<td>If Yes, the document will be immediately removed from the PEBC website, and a note as to its status put in its place. Go to 2.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. On initial review,</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Does the newly identified evidence support the existing recommendations?</td>
</tr>
<tr>
<td>2.a. No</td>
</tr>
<tr>
<td>b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?</td>
</tr>
<tr>
<td>2.b. No</td>
</tr>
<tr>
<td>If both are Yes, the document can be <strong>ENDORSED</strong>. If either is No, go to 3.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.Yes – with delay</td>
</tr>
<tr>
<td>If Yes, a final decision can be <strong>DELAYED</strong> up to one year. If No, go to 4.</td>
</tr>
</tbody>
</table>
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?

<table>
<thead>
<tr>
<th>Review Outcome</th>
<th>Update Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSG/GDG Approval Date</td>
<td>NA</td>
</tr>
<tr>
<td>DSG/GDG Commentary</td>
<td>It was decided that economic reviews are not part of the evidence base required for a treatment guideline and so were not included.</td>
</tr>
</tbody>
</table>

4. Yes

If Yes, the document needs an **UPDATE**. It can be listed on the website as IN REVIEW for one year. If a full update is not started within the year, it will be automatically **ARCHIVED**. If NO, go to 5.

5. If Q2, Q3, and Q4 were all answered NO, this document should be **ARCHIVED** with no further action.
New References Identified:


Literature Search Strategy:

**MEDLINE**

1. meta-Analysis as topic.mp.
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthesis? or quantitative overview?).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (random$i control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
41. exp lymphoma/
42. fludara*.mp.
43. fludarabine.mp.
44. or/42-43

**MEDLINE CONT'D**

45. 41 and 44
46. "high dose chemotherapy".tw.
47. ("transplant" or "stem cell").tw.
48. 45 not (or/46-47)
49. (follicular or "low grade non*hodgkin's").tw.
50. Waldenstrom Macroglobulinemia.tw.
51. 48 and 49
52. 48 and 50
53. 45 and (or/49-50)
55. 53 and 54
56. remove duplicates from 55
EMBASE
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
4. (systematic adj (review$1 or overview$1)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliography$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. exp lymphoma/
37. fludara*-mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
38. fludarabine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
39. or/37-38
40. 36 and 39
41. "high dose chemotherapy”.tw.

**EMBASE CONT’D**

42. ("transplant**” or "stem cell”).tw.
43. 40 not (or/41-42)
44. (follicular or "low grade non* hodgkin’s").tw.
45. Waldenstrom Macroglobulinemia.tw.
46. 43 and 44
47. 43 and 45
48. or/46-47
49. 40 and (or/44-45)
51. 49 and 50
52. remove duplicates from 51
53. limit 52 to english

**CLINICAL TRIALS(clinicaltrials.gov)**
Fludarabine AND Lymphoma – 352 trials returned.

**ASCO**
Fludarabine AND Lymphoma NOT transplant – 220 abstracts

**ASH**
Fludarabine AND Lymphoma – 671 abstracts

**SAGE GUIDELINES**
Current; Hematologic; treatment; guidelines – 156 guidelines

**Cochrane**
Fludarabine AND Lymphoma – 17 Systematic Reviews/Meta-Analyses
OUTCOMES DEFINITION

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word “ARCHIVED”.

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DELAY** – A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.