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Evidence-based Series 6-7 Version 2 – EDUCATION AND INFORMATION 2016

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

The Use of Chemotherapy and Growth Factors in Older Patients with Newly Diagnosed, Advanced-Stage, Aggressive Histology Non-Hodgkin's Lymphoma

T. Kouroukis, G. Browman, and R. Meyer

An assessment conducted in November 2016 put Evidence-based Series (EBS) 6-7 Version 2 in the Education and Information Section. This means that the recommendation will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document.
(PEBC Assessment & Review Protocol)

EBS 6-7 Version is comprised of 3 sections

and is available on the CCO Website on the PEBC Hematology page

Section 1: Clinical Practice Guideline (ENDORSED)
Section 2: Evidentiary Base
Section 3: Document Review Summary and Review Tool

Release Date: June 13, 2013

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version June 2003	1966-2001	Full Report	Web publication Journal publication	NA
Current Version 2 June 2013	2001-2013	New data found in section 3: Document Review Summary and Tool	Updated Web publication	2003 recommendations is **ENDORSED**

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The Use of Chemotherapy and Growth Factors in Older Patients with Newly Diagnosed, Advanced-Stage, Aggressive Histology Non-Hodgkin's Lymphoma

T. Kouroukis, G. Browman, and R. Meyer

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 3: Document Review Summary and Review Tool for a summary of updated evidence published between 2001 and 2013, and for details on how this Clinical Practice Guideline was ENDORSED.

Report Date: May 24, 2013

Guideline Questions

1. What treatment provides the optimum disease control and survival in older patients (at least 60 years of age) with newly diagnosed, advanced-stage, aggressive histology lymphoma?
2. What are the toxicities associated with these treatments?
3. What are the roles of granulocyte-colony stimulating factor or granulocyte macrophage-colony stimulating factor in combination with chemotherapy in these patients?

Target Population

These recommendations apply to patients older than age 60 who have newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma, an Eastern Cooperative Oncology Group (ECOG) performance status of less than 4 and no significant comorbid illnesses.

Recommendations

- Combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) is recommended for patients with no apparent cardiac disease or significant comorbidity. Dose and schedule should be the same as that used in younger patients.
- The addition of rituximab to CHOP is recommended for patients with diffuse large B-cell lymphoma.
- There is insufficient evidence to support the routine use of granulocyte-colony stimulating factor as primary therapy.

- While use of granulocyte-colony stimulating factor shortens the duration of neutropenia and decreases the infection rate in these patients, no differences in disease control or survival have been detected.
- The primary use of granulocyte-colony stimulating factor is recommended for older patients who are at a particularly high risk of experiencing neutropenic fever. These patients are best identified as those with a poor performance status (ECOG 2 or greater), neutropenia prior to therapy, or an ongoing infection; there are insufficient data to recommend the primary use of granulocyte-colony stimulating factor for patients whose sole risk factor is bone marrow involvement with lymphoma.
- The use of granulocyte-colony stimulating factor as secondary prophylaxis is recommended for patients who have previously experienced an episode of neutropenic fever or a treatment delay resulting from persisting neutropenia.

Qualifying Statements

- Treatment decisions in older patients with aggressive histology lymphoma are complex and may be influenced by comorbidity, patient preferences, quality of life issues, and the goals of the treatment program. These factors may alter recommendations for individual patients and require discussion between health care providers, patients, and their families.
- Radiation therapy is not considered in this guideline and may be an important part of the treatment plan for these patients.

Methods

A systematic search was undertaken of MEDLINE (1966 through January 2002 Week 2), CANCERLIT (1983 through October 2001), EMBASE (1980 to October 2001), Current Contents (1993 to October 2001), the Cochrane Library (Issue 4, 2001), *Best Evidence* (1991 to October 2001), Physician's Data Query clinical trials database, a database of unpublished theses (UMI ProQuest®), relevant conference proceedings, and tables of contents for relevant journals. Reference lists were also scanned for additional citations. For the question regarding chemotherapy, we reviewed randomized studies comparing different chemotherapy regimens in patients 60 years of age and older with newly diagnosed, advanced-stage, aggressive histology lymphoma. Randomized studies of granulocyte-colony stimulating factor and granulocyte macrophage-colony stimulating factor encompassing the same patient population were also reviewed. Overall, progression-free, event-free and relapse-free survival, toxicity, quality of life, economic analyses, and response rates were the outcomes of interest.

Evidence was selected and reviewed by four 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 comprises hematologists, medical oncologists, radiation oncologists, methodologists, and a patient representative.

External review by Ontario practitioners was initially obtained through a mailed survey for the original draft recommendations in August 2000. Because of new data that emerged during this review process, completion of the original guideline report was deferred. External review of the revised guideline report by Ontario practitioners was also obtained through a mailed survey. Final approval of the guideline report was obtained from the Practice Guidelines Coordinating Committee.

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

Key Evidence

- A total of 23 publications (13 full papers and ten abstracts) and two systematic reviews form the basis of evidence for the chemotherapy question. An additional five publications (two practice guidelines, one full paper, and two abstracts) provide evidence for the growth factors section.

- In a randomized trial comparing CHOP with a regimen considered to be less toxic (etoposide, mitoxantrone and prednimustine [VMP]), progression-free and overall survival were superior in the group receiving CHOP.
- In a randomized trial comparing a CHOP-like regimen, in which pirarubicin is substituted for doxorubicin and teniposide is substituted for vincristine (CTVP), with a regimen considered to be less toxic (cyclophosphamide, teniposide and prednisone [CVP]), progression-free and overall survival were superior in the group receiving CTVP.
- In a randomized trial comparing CHOP with a fractionated schedule of weekly CHOP, overall survival was superior in the group receiving standard CHOP.
- In two randomized trials comparing CHOP with a regimen in which mitoxantrone was substituted for doxorubicin (CNOP), progression-free and overall survival were superior in the groups receiving CHOP. In a third randomized trial in which a weekly doxorubicin- containing regimen was compared with a regimen in which mitoxantrone was substituted for doxorubicin, response rate and overall survival were superior in the group receiving the mitoxantrone-containing regimen. The investigators of this study are currently conducting a randomized trial in which the weekly mitoxantrone-containing regimen is compared with CHOP.
- In a randomized trial comparing CHOP to a combined regimen of rituximab and CHOP, event-free and overall survival were superior in the group receiving CHOP plus rituximab.
- In three randomized trials evaluating the primary use of granulocyte-colony stimulating factor, no differences between the randomized groups were detected in disease control or overall survival. Less severe granulocytopenia and fewer infections and days of antibiotic use were observed in patients receiving granulocyte-colony stimulating factor.

Related Guidelines

- Practice Guidelines Initiative's Practice Guideline Report #12-2: *Use of Granulocyte Colony-Stimulating Factor (G-CSF) in Patients Receiving Myelosuppressive Chemotherapy for the Treatment of Cancer.*
- Evidence-Based Series #6-8: *Rituximab in Lymphoma and Chronic Lymphocytic Leukemia Update: A Clinical Practice Guideline.*

For further information about this practice guideline report, please contact: Dr. Ralph Meyer, Chair, Hematology Disease Site Group, 699 Concession Street, Hamilton, Ontario, L8V 5C2; TEL (905) 525-7820; FAX (905) 575-6340.

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

Visit www.ccopebc.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 (PEBC). 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:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgement in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

Glossary of Chemotherapy Regimens

ACVBP (1)[a]: Doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone, intrathecal methotrexate

ASHAP-mBACOS-MINE (2): Doxorubicin, methylprednisolone, cytarabine, platinum, methotrexate, bleomycin, cyclophosphamide, vincristine

BEP (3): BCNU (carmustine), etoposide, procarbazine

CEOP-B (4): Cyclophosphamide, epirubicin, vincristine, methylprednisolone, bleomycin

CEOP-Bleo (5): Cyclophosphamide, epirubicin, vincristine, prednisone, bleomycin

CEP (6): Cyclophosphamide, etoposide, prednisolone

CEVOP (7): Cyclophosphamide, epirubicin, etoposide, vincristine, prednisone

CIOP-B (5): Cyclophosphamide, idarubicin, vincristine, prednisone, bleomycin

CHOP (8): Cyclophosphamide, doxorubicin, vincristine, prednisone

CHOP-B (4): Cyclophosphamide, doxorubicin, vincristine, methylprednisolone, bleomycin

CHOP-R (9): Cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab

CHOEP (10): Cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone

CNOP (11): Cyclophosphamide, mitoxantrone, vincristine, prednisone

CTVP (12): Cyclophosphamide, pirarubicin, teniposide, prednisone

CVP (12): Cyclophosphamide, teniposide, prednisone

CVP (6): Cyclophosphamide, vindesine, prednisolone

ISHAP-mBICOS-MINE (2): Idarubicin, methylprednisolone, cytarabine, platinum, methotrexate, bleomycin, cyclophosphamide, vincristine

MACOP-B (13): Methotrexate, doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone

m-BACOD (14): Methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisone

MEP (3): Mitoxantrone, etoposide, procarbazine

MiCEP (15): Mitoxantrone, etoposide, cyclophosphamide, prednisone

PAdriCEBO (16): Prednisolone, doxorubicin, cyclophosphamide, etoposide, bleomycin, vincristine

PMitCEBO (16): Prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine

ProMACE-CytaBOM (17): Cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate, prednisone

ProMECE-CytaBOM (18): Cyclophosphamide, epirubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate, prednisone

PVABEC (15): Etoposide, doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone

P-VEBEC (19): Epirubicin, cyclophosphamide, etoposide, vinblastine, bleomycin, prednisone

T-COP (20), THP-COP (21): Pirarubicin, cyclophosphamide, vincristine, prednisone

THP-COPE (21): Pirarubicin, cyclophosphamide, vincristine, prednisone, etoposide

VMP (22): Etoposide, mitoxantrone, prednimustine

VNCOP-B (23): Cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, prednisone

[a]Reference numbers

Ontario
Cancer Care Ontario
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Evidence-based Series #6-7 version 2: Section 2

The Use of Chemotherapy and Growth Factors in Older Patients with Newly Diagnosed, Advanced-Stage, Aggressive Histology Non-Hodgkin's Lymphoma

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Report Date: May 24, 2012

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making.
Please see Section 3: Document Review Summary and Review Tool for a summary of updated evidence published between 2001 and 2013, and for details on how this Clinical Practice Guideline was ENDORSED.

I. QUESTIONS

1. What treatment provides the optimum disease control and survival in older patients (at least 60 years of age) with newly diagnosed, advanced-stage, aggressive histology lymphoma?
2. What are the toxicities associated with these treatments?
3. What are the roles of granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF) in combination with chemotherapy in these patients?

II. CHOICE OF TOPIC AND RATIONALE

The numbers of elderly persons are increasing and are soon expected to make up 20% of the population in North America (24). One-half of patients with aggressive histology lymphoma are older than 65 years (25). Age is known to be a powerful prognostic factor for overall survival for patients with aggressive histology lymphoma (26). Until recently, patients older than 65 have been under-represented in clinical trials, and most conclusions about the best chemotherapy for these patients have not been based on direct evidence. Outcomes of older patients with lymphoma may differ from those of younger patients due to alterations in disease biology and poorer tolerance of standard chemotherapeutic regimens. Biological age plays a more important role than chronological age, and compromises in response and survival may occur if suboptimal chemotherapy is given to patients with chemosensitive lymphoma (27-30).

The members of the Hematology Cancer Disease Site Group (Hematology DSG) suspected that the selection of chemotherapy for this group of patients varied across Ontario. The availability of recent evidence, the perceived variability in practice patterns, and the potential for this variation to influence the outcomes of older patients led to the development of this topic as a practice guideline. The few published guidelines for patients with lymphoma (31-33) have either not specifically focused on the treatment of older patients (32) or have not used systematic review methodology in their data collection (31;33). Two published guidelines (34-36) and one expert panel review (37) for the use of colony stimulating factors in patients with malignancy have made recommendations in patients receiving myelosuppressive chemotherapy but do not address the older population specifically. The Hematology DSG felt it appropriate to appraise studies on the use of colony stimulating factors in older patients to see whether suggestions should differ from those already published. This guideline will, therefore, address both the optimum choice of primary therapy and the role of granulocyte- (or granulocyte-macrophage) colony stimulating factor when treating older patients with aggressive histology lymphoma. The role of radiation therapy may also be an important part of the overall treatment plan for these patients but will not be addressed in this document.

A previous version of this guideline report was circulated for practitioner feedback in August 2000. Based on the practitioner feedback and the availability of new data, the document was revised and recirculated for practitioner feedback. Portions of this guideline have been published as a systematic review of full paper publications of chemotherapy trials for older patients with aggressive histology lymphoma (38).

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 methods of the Practice Guidelines Development Cycle (39). Evidence was selected and reviewed by four 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 chemotherapy and growth factors in older patients with newly diagnosed aggressive histology lymphoma, 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 Practice Guidelines Initiative 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 consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

Searches were performed without language restriction in the following databases: PreMEDLINE & MEDLINE (1966 through January 2002, Week 2), CANCERLIT (1983 through October 2001), EMBASE (1980 to October 2001), Current Contents (1993 to October 2001), the Cochrane Library (Issue 4, 2001), *Best Evidence* (1991 to October 2001) and an unpublished theses database (UMI ProQuest®(40)). The following terms were used for MEDLINE and CANCERLIT: "lymphoma, non-Hodgkin" (MESH, text word), "lymphoma" (text word) combined with "aged" (text word) or "older" (text word) combined with "chemo:" (text word). These terms were then combined with search terms

for the following study designs: practice guidelines, systematic reviews, meta-analyses, and randomized controlled trials. The detailed search strategy has been described in Appendix I.

Bibliographies of major textbooks, review articles, and primary studies were hand searched. Conference proceedings of the American Society of Hematology (1993-2001), American Society of Clinical Oncology (1993-2001), International (Lugano) Conference on Malignant Lymphoma (1996, 1999), and the European Cancer Conference (ECCO 1995, 1997, 1998, 2001) were searched. A manual review of the table of contents was performed for the following journals from 1993 to 1998: *American Journal of Hematology, Annals of Oncology, Blood, British Journal of Hematology, Cancer, European Journal of Cancer, European Journal of Hematology, Journal of Clinical Oncology,* and the *New England Journal of Medicine*. The Physician's Data Query (PDQ, National Cancer Institute, USA) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for trials in progress using the terms "non-Hodgkin's lymphoma, adult" and "chemotherapy".

A separate search for studies assessing risk factors predictive of fever and neutropenia in elderly lymphoma patients was undertaken to assist the Hematology DSG in evaluating the role of primary prophylaxis with growth factors. The following terms were searched in MEDLINE (1966 through September 2001) and CANCERLIT (1984 through September 2001): "lymphoma, non-Hodgkin" (MESH, textword), "lymphoma" (textword) combined with "neutropenia" (textword) and "risk factor" (textword). Abstract publications were not included. Specific parameters to assess the quality of these studies were not applied.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized controlled trials (RCTs) involving newly diagnosed patients with aggressive histology [intermediate- and high-grade, Working Formulation (41)] lymphoma who were 60 years of age and older. The age threshold of 60 years was chosen in order to remain consistent with the findings of the International Prognostic Index (IPI) (26).

1. To assess the role of chemotherapy, RCTs must compare at least two chemotherapy regimens.
2. To assess the role of colony stimulating factors, RCTs comparing the use of G-CSF or GM-CSF with a control group were sought. In the initial phase of this guideline, non-randomized studies utilizing colony stimulating factors that included at least ten patients (chosen arbitrarily) were also eligible. These trials were subsequently made ineligible in February 2001 when data from three randomized trials became available.
3. Randomized studies assessing the use of monoclonal antibodies (e.g., rituximab) were eligible.
4. Subgroup analyses based on age or histology were eligible.

The outcome measures of interest included at least one of the following: overall survival (OS), disease-free (DFS) or failure-free survival (FFS), time-to-treatment failure (TTF), relapse-free survival (RFS), response rate, toxicity, or quality of life measures.

Exclusion Criteria

Studies were excluded if:

1. Patients included had indolent lymphoma, refractory or relapsed lymphoma, human immunodeficiency virus (HIV) related lymphoma, Hodgkin's disease, multiple myeloma, or other hematological malignancies;
2. Transplantation, maintenance chemotherapy, or interferon were used as interventions; or
3. Radiation therapy was used unevenly in experimental and control groups.

Studies assessing the role of chemotherapy were excluded if they incorporated growth factors as part of the primary therapy in all randomized groups. Also, letters and editorials were not considered.

Risk Factors for Fever and Neutropenia

Responses obtained in the first external review by Ontario practitioners of the initial draft version of the evidence-based recommendations supported a need to review and clarify recommendations regarding the use of hematopoietic growth factors for primary prophylaxis to prevent fever with neutropenia. Subsequently, new data assessing the use of growth factors became available. To better evaluate the potential role of primary prophylaxis, the DSG determined that a separate analysis limited to elderly lymphoma patients assessing risk factors that predict for fever with neutropenia and treatment-related mortality would be helpful.

Article Selection

Citations were blinded for authors, journal name, institution, and results by one author. An assessment was made by two independent observers who scored each blinded citation as: "yes" (inclusion criteria were met, no exclusion criteria were met); "no" (one or more exclusion criteria were met); or "maybe" (unclear from citation if article meets any criteria). The full-length article was retrieved if the citation scored "yes" or "maybe" by at least one observer. Inclusion and exclusion criteria were applied again to the full article if necessary. Interobserver kappa coefficients (quadratic weighted) were calculated using PCAgree© (42) for the MEDLINE, CANCERLIT, and EMBASE databases, and an intraobserver coefficient was calculated from a random sample (random numbers table) of twenty MEDLINE citations for the citations assessing the role of chemotherapy. Acceptable kappa coefficients were 0.60 or greater (43). The citation lists for subsequent search updates were reviewed by one author using the same inclusion/exclusion criteria outlined previously.

Study Quality Assessment

Methodological assessment was performed using the published validated quality assessment tool of Jadad et al. for randomized controlled trials (44), but the score was not used to explicitly weight study results or to exclude studies from the analysis. This scale assigns one point if the study is randomized, one point if it is double-blinded, and another point if there is a complete description of withdrawals. An additional point each may be awarded if the randomization and the blinding were done appropriately. Studies may therefore score from zero to five points. It has been shown that studies scoring 2 points or less on this scale are more likely to produce treatment effects that are on average 35% larger than those produced by trials scoring 3 points or more (45). Randomized trials were also assessed based on whether the study population was explicitly defined, how baseline characteristics of the randomized groups compared, whether primary and secondary outcome measures and minimum important differences were stated, how the target sample size was projected (46), whether an intention-to-treat analysis was performed (47), whether randomization was concealed, whether co-interventions and endpoints were explicitly stated, and whether appropriate statistics were used.

Fully published articles are generally required in order to be most confident that the methodological assessment has identified the strengths and weaknesses of the trials. Most abstracts provide information of a more preliminary nature that may result in a lesser degree of confidence in making treatment recommendations. Subset analyses, while providing information of a hypothesis-generating nature, may be potentially misleading (48) and thus provide limited information for devising treatment recommendations. Therefore, conclusions about the use of chemotherapy and growth factors are most influenced by the full paper publications of primary studies.

Synthesizing the Evidence

Pooling trial results for both the chemotherapy and colony stimulating factor trials was considered but was not feasible. The nature of the chemotherapy regimens tested was very heterogeneous, making meaningful results from pooling impossible. Pooling of outcomes for studies assessing G-CSF was also considered but was not feasible because of the differences in outcome measurement assessed and the timing of assessment. Where p values were missing in individual

studies, the appropriate statistical test was done using the Statistical Package for the Social Sciences (version 8.0, SPSS Inc., Chicago, IL) (49).

IV. RESULTS

Literature Search Results

Two hundred and eighty-nine publications were initially identified from MEDLINE, 106 publications from CANCERLIT, 376 from EMBASE and 52 from Current Contents for the chemotherapy question, up to 1999. No additional appropriate publications were found by searching the thesis database, Best Evidence, or the Cochrane Library. Six abstracts were found by hand searching. After removing duplicate citations and those dealing exclusively with Hodgkin's disease, myeloma, leukemia, or younger patients, a total of 385 blinded citations were assessed by two independent reviewers. This search was updated in 2001 and 2002. Including the updated searches, 23 publications (13 full papers, 10 abstracts) met the eligibility criteria for chemotherapy trials and were included. Two systematic reviews were also found (38;50), one of which represents a portion of this document published as a systematic review (38).

From the initial search for studies assessing the role of growth factors, 246 citations were found in EMBASE, 421 in MEDLINE, 130 citations in CANCERLIT, and 25 in Current Contents. No additional relevant publications were found by searching the thesis database, Best Evidence, or the Cochrane Library. Three abstracts were found by hand searching. Two independent reviewers assessed a total of 293 blinded citations. This search was also updated in 2001 and 2002. In the updated searches, five articles were reviewed for this section: two practice guidelines, one full-length paper, and two abstracts. Table 1 summarizes the reasons that publications were excluded based on the original searches. The search for risk factors for febrile neutropenia and treatment-related mortality resulted in 955 citations that were reviewed by one author.

Table 1. Reasons for study exclusion (number of studies).

Reason	Chemotherapy search	Colony stimulating factors search
Other diseases (myeloma, Hodgkin's, leukemia, etc.)	78	101
Other interventions	72	21
Wrong study design	56	40
Low grade, relapsed/refractory NHL	44	26
Transplantation/growth factor use (chemo search only)	75	78
No age subgroup analysis	56	44
Basic science	22	36
Patients too young	6	2
HIV	9	3
Published in full later	3	3
Review article	59	15
Total	480[a]	394[a]

Note: NHL=non-Hodgkin's lymphoma and HIV=human immunodeficiency virus.
[a]duplicate studies already excluded; for literature search ending in 1999.

Agreement Statistics

The interobserver weighted kappa was 0.74 for the chemotherapy citations. The intraobserver weighted kappas for the random sample of 20 MEDLINE chemotherapy citations were 0.60 (reviewer 1) and 0.80 (reviewer 2). The interobserver weighted kappa was 0.82 for the colony stimulating factor citations. These represent adequate agreement coefficients (43).

Quality Assessment Scores

Of the 23 studies assessing the role of chemotherapy (Table 2), three scored 3 on the Jadad quality scale (11;22;51), ten scored 2 (4;5;7;12;16;18;52-55) and ten scored 1 (1;2;6;10;15;20;21;56-

58). The studies assessing the use of colony stimulating factors scored 2 points (23) and 1 point (57;59). One study assessing the role of rituximab scored 2 points (9).

Outcomes

Chemotherapy

A total of 23 publications (1-7;10-12;15;16;18;20-22;51-55;57;58) and two systematic reviews (38;50) were identified that addressed the chemotherapy guideline question. One systematic review (50) contained a section on elderly patients with lymphoma; however, it was not explicit about the individual studies included, and the majority of studies present in this practice guideline report were not identified or discussed. The other systematic review was the published chemotherapy review portion of this practice guideline report (38), which only included full paper publications of randomized trials and not abstract reports.

The studies testing various chemotherapy regimens fell into one of three general categories: (a) those comparing regimens that differed only in the type of anthracycline used; (b) those comparing different chemotherapy schedules; and (c) those comparing chemotherapy regimens that differed by other parameters (Table 2).

Table 2. Categories of randomized studies for chemotherapy question.

Study Category		First author, year, (reference), type of publication
Comparison of regimens that differ only in the anthracycline		Mainwaring, 2001 (16), full paper[a] Björkholm, 1999 (57), abstract[a] Aoki, 1998 (52), full paper Avilés, 1997 (5), full paper Cabanillas, 1997 (2), abstract[a] Sonneveld, 1995 (11), full paper Kitamura, 1994 (21), abstract[a] Delena, 1989 (4), subgroup analysis
Comparison of regimens with different schedules		Pfreundschuh, 2001 (10), abstract[ab] Soubeyran, 1998 (7), abstract[a] Meyer, 1995 (53), full paper
Other	CHOP versus other regimens	Pfreundschuh, 2001 (10), abstract[ab] Tilly, 2000 (1), abstract[a] Tirelli, 1998 (22), full paper Montserrat, 1996 (58), subgroup analysis Cooper, 1994 (51), subgroup analysis Gaynor, 1994 (54), abstract[a] Gordon, 1992 (55), subgroup analysis
	Different regimens that do not include CHOP	Delwail, 2000 (6), abstract[a] Jelić, 1999 (3), full paper Bastion, 1997 (12), full paper Bellesi, 1996 (15), abstract[a] Silingardi, 1995 (18), subgroup analysis
	Dose intensity of same regimen	Kitamura, 1998 (20), abstract[a]

[a]not included in the published systematic review (38).
[b]appears twice in table.

(a) *Comparison of regimens that differ only in the anthracycline*

This category consists of eight studies: five full papers (4;5;11;16;52) and three abstracts (2;21;57). None of the studies were blinded, only one described the randomization method (11), and

none made any comments with respect to concealment. The full papers had complete descriptions of subject withdrawals, but the abstracts did not. The studies are summarized in Tables 3 and 4.

Mainwaring et al. (16) randomized 473 patients 60 years of age and older to a doxorubicin- (35 mg/m^2) or a mitoxantrone-containing (7 mg/m^2) weekly combination regimen (PAdriCEBO v. PMitCEBO). Up to 40 percent of patients had stage I or II disease, and 66 percent had a World Health Organization (WHO) performance status of less than 2. The overall response rate was superior in patients receiving the mitoxantrone-containing regimen (Table 4). Although no difference in RFS was detected, four-year OS was superior in patients randomized to the mitoxantrone-containing regimen (Table 4). A multivariate analysis of prognostic factors in this trial identified the chemotherapy regimen, age greater than 70, advanced stage, and poor performance status as significant factors for survival.

Björkholm et al. (57) reported on 455 patients aged 60 years of age and older randomized to CHOP or CNOP as part of a factorial design also involving G-CSF. Patients receiving CHOP had improved OS compared with those receiving CNOP (Table 4), but groups did not differ for complete response (CR) (Table 4).

Aoki et al. (52) randomized 37 patients to low doses of CHOP or to one of two pirarubicin-based regimens (THP-COP or THP-COPE). Seven patients (19%) were subsequently withdrawn due to ineligibility and protocol violations, and the analysis was based on the remaining 30 patients. The overall response rate was similar among patients receiving low dose CHOP, THP-COP, and THP-COPE (Table 4). There was no significant difference in two-year OS (Table 4; p value not stated).

Avilés et al. (5) randomized 169 patients to receive either CEOP-Bleo (epirubicin-based) or CIOP-Bleo (idarubicin-based) with escalating doses of the anthracycline. The group receiving the epirubicin-containing regimen had a superior CR rate (Table 4) and three-year OS (Table 4). There is a potential concern regarding patients who were excluded from the analysis if they experienced more than a two-week delay in chemotherapy administration. In addition, the study recorded no treatment-related mortality.

Sonneveld et al. (11) tested whether the substitution of doxorubicin in CHOP for mitoxantrone (CNOP) improved outcomes in 148 patients 60 years of age and older. Almost half of the patients were less than 70 years, and in contrast to other studies, some degree of cardiac dysfunction (left ventricular ejection fraction at least 40%) was permitted. Patients receiving CHOP had a higher CR rate (Table 4), a superior median OS (Table 4), and a superior three-year OS (Table 4). At three years, 17% of CHOP and 13% of CNOP patients were alive and disease-free (p=0.12). Patients receiving CHOP experienced significantly more alopecia (p<0.001), nausea (p=0.02), and vomiting (p=0.02).

The remaining studies (2;4;21) are summarized in Tables 3 and 4. Conclusions from these studies are limited due to lack of details reported in the papers.

Table 3. Randomized trials comparing chemotherapy regimens that differ only in the anthracycline: patients and therapy.

Study, type of publication and analysis	Patient characteristics				Intervention	
	Age (y)	N	Stage	Pathology	Regimens[a]	Principle tested
Mainwaring (16) Full, primary	≥60	473	IB-IV	DLC, IM, DM	PAdriCEBO v. PMitCEBO	substitution of doxorubicin for mitoxantrone
Björkholm (57) Abstract, primary	≥60	229	II-IV	HG	CHOP v. CNOP	substitution of mitoxantrone for doxorubicin
Aoki (52) Full, primary	≥65	37	I-IV	FMC, DSC, DM, DLC, DP	LD-CHOP v. THP-COP v. THP-COPE	substitution of doxorubicin for pirarubicin and the addition of etoposide
Avilés (5) Full, primary	≥60	169	NS	DLC, SNCC, IM, ALCL	CEOP-B v. CIOP-B	substitution of epirubicin for idarubicin

Cabanillas (2) Abstract, primary	>60	52	NS	MD Anderson tumor score ≥3	ASHAP-mBACOS-MINE v. ISHAP-mBICOS-MINE	substitution of doxorubicin for idarubicin
Sonneveld (11) Full, primary	≥60	148	II (bulky), III, IV	DM, DLC, IM	CHOP v. CNOP	substitution of mitoxantrone for doxorubicin
Kitamura (21) Abstract, primary	≥65	420	NS	NS	LD-CHOP v. THP-COP v. THP-COPE	substitution of doxorubicin for pirarubicin and the addition of etoposide
Delena (4) Full, subgroup	≥60	24	any bulky with B symptoms	IG or HG (WF)	CHOP-B v. CEOP-B	substitution of epirubicin for doxorubicin

Note: ALCL= Anaplastic large cell lymphoma, DLC=diffuse large cell, DM=diffuse mixed, DP=diffuse pleomorphic, DSC=diffuse small cell, FMC=follicular medium cell, HG=high-grade, IG=intermediate grade, IM=immunoblastic, LD=low dose, NS=not specified, SNCC=small non-cleaved cell, v.=versus, WF=Working Formulation.
[a]Please refer to glossary for full names of chemotherapy regimens.

Table 4. Randomized trials comparing chemotherapy regimens that differ only in the anthracycline: results.

Study/Comparison	Results[a]		
	Response rate	**Disease control**	**Overall Survival**
Mainwaring (16) PMitCEBO v. PAdriCEBO	CR 60% v. 52% (p=0.12) OR 78% v. 69% (p=0.05)	RFS 59% v. 38% (p=0.16)	OS (4y) 50% v. 28% (p=0.0067)
Björkholm (57) CHOP v. CNOP	CR 59% v. 46% (p=0.08)[b]	NR	OS[c] (median) 38 m v. 13 m; (5y) 42% (95% CI 31-53%) v. 28% (95% CI 19-36%)
Aoki (52) LD-CHOP v. THP-COP v. THP-COPE	OR 63.6% v. 80% v. 87.5% (p=0.3)[b]	NR	OS (2y) 18% v. 58% v. 48%
Avilés (5) CEOP-B v. CIOP-B	CR 71% v. 48% (p=.003)[b]	NR	OS (3y) 72% v. 34% (p<0.01)
Cabanillas (2) ASHAP-mBACOS-MINE v. ISHAP-mBICOS-MINE	CR 68% v. 54% (p=0.2)	FFS (3 y) 39% v. 27% (p=0.17)	OS (3y) 49% v. 35% (p=0.07)
Sonneveld (11) CHOP v. CNOP	CR 49% v. 31% (p=0.03)	DFS (median) 27 m v. 15 m (p=0.43); (3y) 17% v. 13% (p=0.12)	OS (median) 26 m v. 12 m (p=0.029); (3y) 42% v. 26% (p=0.034)
Kitamura (21) LD-CHOP v. THP-COP v. THP-COPE	CR 44.3% v. 45.1% v. 49.7% (p=ns)	NR	CR patients (median 3y follow-up) 42% v. 72% v. 59% (p=0.03 for CHOP v. THP based chemotherapy)
Delena (4) CHOP-B v. CEOP-B	CR 50% v. 71% (p=0.4)[b]	NR	NR

Note: CR=complete response, CI=confidence interval, DFS= disease-free survival, FFS=failure-free survival, LD=low dose, m=months, NR=not reported, ns=not significant, OR=overall response, OS=overall survival, RFS=relapse-free survival, v.=versus, y=years.
[a]results shown in same order as chemotherapy regimens presented.
[b]Chi-square p-value calculated from data reported.
[c]Hazard ratio 0.53, 95% CI 0.41 to 0.68; p<0.001.

Interpretive summary for this category

This category contains studies with varied results. All studies included patients who were free of important comorbid illness. Two large studies (11;57) showed a survival benefit of doxorubicin compared with mitoxantrone when given in CHOP. When doxorubicin was compared with mitoxantrone in a non-CHOP-like, multi-agent chemotherapy regimen that was administered on a weekly basis, there was a survival benefit for patients receiving the mitoxantrone-based regimen (16). This study contained a higher proportion of patients with limited stage (I and II) disease. The remaining studies examining epirubicin, pirarubicin and idarubicin-based regimens were limited due to: concerns about the reporting of patient withdrawals and the lack of treatment-related mortality data (5); small

numbers of patients; lack of an intention-to-treat analysis; use of less than standard doses of CHOP (52); lack of survival data (4); and reporting of subgroup analyses (2).

(b) Comparison of regimens with different schedules

This category contains three studies: one full paper (53) and two abstracts (7;10). The studies were not blinded and did not mention the method of randomization or concealment. The studies are summarized in Tables 5 and 6.

Table 5. Randomized trials comparing chemotherapy regimens with different schedules: patients and therapy.

Study, type of publication and analysis	Patient characteristics				Intervention	
	Age (y)	N	Stage	Pathology	Regimens[a]	Principle tested
Pfreundschuh (10) Abstract, primary	>60	809	NS	NS	CHOP v. CHOP-14	G-CSF day 4-recovery
Soubeyran (7) Abstract, primary	>65	37	NS	IG, HG (WF)	CEVOP-I v. CEVOP-II	weekly schedule fractionation
Meyer (53) Full, primary	≥65	38	IB, IIA(bulky), IIB, III, IV	FLC, DSCC, DM, DLC, IM	CHOP v. chop[b]	weekly schedule fractionation

Note: DLC=diffuse large cell, DM=diffuse mixed, DSCC=diffuse small cleaved cell, FLC=follicular large cell, HG=high-grade, IG=intermediate grade, IM=immunoblastic, NS=not specified, v.=versus, WF=Working Formulation.
[a]Please refer to glossary for full names of chemotherapy regimens.
[b]Conventional scheduled CHOP was compared with one-third dose administered weekly (chop).

Table 6. Randomized trials comparing chemotherapy regimens with different schedules: results.

Study/Comparison	Results[a]		
	Response rate	Disease control	Overall Survival
Pfreundschuh (10) CHOP-14+G-CSF v. CHOP	CR 77% v. 63.2% (p=0.055)[b]	TTF (40 m) 53.4% v. 42.5% (p=0.03)	OS (40 m) 64.3% v. 49% (p=0.04)
Soubeyran (7) CEVOP-I v. CEVOP-II	CR 65% v. 55.5% (p=0.8)[c]	NR	NR
Meyer (53) CHOP v. chop	CR 68% v. 74% (p=0.9)	PFS (2 y) 57% v. 46% (p=0.16)	OS (2 y) 74% v. 51% (p=0.05)

Note: CR=complete response, m=months, NR=not reported, OS=overall survival, PFS=progression-free survival, TTF=time-to-treatment failure, v.=versus, y=years.
[a]results shown in same order as chemotherapy regimens presented.
[b]for comparison across all groups.
[c]Chi-square p-value calculated from data reported.

Compression

Pfreundschuh et al. (10) reported results of a four-arm randomized trial evaluating patients 61 to 75 years of age with aggressive histology lymphoma and comparing CHOP administered either every 21 days or 14 days and CHOP plus etoposide (CHOEP) also administered every 21 days or 14 days. Patients receiving either 14-day regimen (i.e., CHOP-14 or CHOEP-14) also received G-CSF. The trial was to be analyzed using a factorial design in order to assess the effect of compressing the treatment schedule and the addition of etoposide. Because of an interaction between the addition of etoposide and schedule compression, in which patients receiving CHOEP every 14 days experienced excessive toxicity, the trial was instead analyzed as a four-armed comparison using a Cox model. With respect to

compressing the treatment schedule, a comparison of outcomes between the CHOP-21 and CHOP-14 groups detected that the CHOP-14 group had a superior 40-month TTF (Table 6) and OS (Table 6), with a trend for improved CR rate (Table 6).

Fractionation

The randomized phase II study by Soubeyran et al. (7) published in abstract form, compared standard and fractionated schedules of CEVOP. No difference was detected in achievement of a CR. The group receiving the fractionated schedule of chemotherapy received therapy of reduced dose intensity, had a higher frequency of treatment interruptions due to toxicity, and reported lower quality of life scores. Specific data were not provided.

A randomized phase II study by Meyer et al. (53) compared the conventional CHOP schedule with one-third doses administered weekly (chop) for the same intended dose-intensity. There were no differences in received dose intensities (primary outcome) when calculated by two different methods (53;60) or in the CR rate between CHOP and chop (Table 6). Although two-year progression-free survival (PFS) was similar between CHOP and chop (Table 6), the two-year OS was of borderline significance in favour of CHOP (Table 6). Apart from more leukopenia in patients randomized to CHOP, there were no statistically significant differences in important toxicities.

Interpretive summary for this category

No benefits from fractionating the treatment schedule have been detected; the potential for outcomes to be inferior is suggested. In a preliminary abstract publication reporting results of compressing the schedule of CHOP from 21 days to 14 days, improvements in disease control and survival are indicated (10). However, the interpretation of this study is limited by the complex statistical analysis and requires a full report in article form for complete assessment.

(c) Comparison of other chemotherapy regimens

This category includes thirteen studies: seven full papers (3;12;18;22;51;55;58) and six abstracts (1;6;10;15;20;54). None of the studies were blinded, only two described the method of randomization (22;51), and none described concealment. The seven full papers (3;12;18;22;51;55;58) and one abstract (54) contained adequate information on patient withdrawals, but this information was lacking in the other abstract reports (1;6;10;15;20). Seven studies compared CHOP with other regimens (1;10;22;51;54;55;58), five studies compared two other regimens (3;6;12;15;18), and one study compared different doses of the same regimen, with dose determined by age stratification (20). These studies are highlighted in Tables 7 and 8.

Of the seven trials comparing CHOP with another regimen, one (22) has been published in article form, three as subgroup analyses (51;55;58), and three in abstract form (1;10;54). A European Organization for the Research and Treatment of Cancer (EORTC) trial (22) randomized 120 patients 70 years of age and older to CHOP or VMP. Patients with a performance status of 2 or 3 were started at 75 percent of the standard chemotherapy dose. Patients who received CHOP had a higher overall response rate (Table 8), a borderline higher CR rate (Table 8), a longer median PFS (Table 8), a longer median OS (Table 8), and an improved four-year OS (Table 8). There was a trend toward more cardiovascular toxicity in patients receiving CHOP; they also experienced more alopecia and gastrointestinal and neurological toxicity.

None of the other publications in this category have reported a survival advantage for patients receiving a treatment that was compared with CHOP. A Group d'Etude des Lymphomes de l'Adulte trial (GELA) (1) randomized 708 patients aged 61-69 years to ACVBP or CHOP. No differences were detected in CR rate or three-year OS. There was an improvement in three-year event-free (Table 8) and disease-free survival (Table 8) in patients randomized to ACVBP. These benefits appear to be offset by an increased treatment-related mortality in patients receiving ACVBP (13% v. 7%; $p<0.01$). A study published in abstract form compared CHOP with CHOP plus etoposide (10) in patients greater than 60 years old. No differences were detected in response rate, TTF, or OS, and the authors

commented that the addition of etoposide was associated with significant toxicity. Four studies (51;54;55;58) compared CHOP with one or more "second or third generation" regimens. In each of these studies, no advantage favouring an experimental arm was detected in any outcome measure. Treatment with MACOP-B was associated with an inferior response rate in one study (51) and inferior OS in another (54).

Five studies (6;12;15;18;56) compared regimens that did not include CHOP, and one study examined dose intensities of the same regimen in older patients of different ages (20); two reports are in article form (12;56). Bastion et al. (12) randomized 453 patients at least 70 years of age to CTVP or CVP. Treatment with CVTP was associated with a superior CR rate (Table 8), median TTF (Table 8), five-year TTF (Table 8), and five-year OS (Table 8) and a lower rate of progressive disease (Table 8). Patients receiving CTVP experienced more alopecia and mucositis and had more frequent and prolonged hospitalizations. The remaining studies (6;15;18;20;56) are summarized in Tables 7 and 8; all contain insufficient information to influence guideline development.

Table 7. Randomized trials comparing other chemotherapy regimens: patients and therapy.

Study, type of publication and analysis	Patient characteristics				Intervention	
	Age (y)	N	Stage	Pathology	Regimens[a]	Principle tested
Pfreundschuh (10) Abstract, primary	>60	807	NS	NS	CHOP v. CHOEP	addition of etoposide to CHOP
Tilly (1) Abstract, primary	61-69	708	≥1 adverse aa-IPI factor (26)	NS	CHOP v. ACVBP	CHOP v. more aggressive chemotherapy
Tirelli (22) Full, primary	≥70	120	II, III, IV	IG, HG (WF) excluding SNCC, LL	CHOP v. VMP	standard v. presumed less toxic chemotherapy
Montserrat (58) Full, subgroup	≥60	78	II, III, IV	FLC,DSCC, DM, DLC, IM	CHOP v. ProMACE-CytaBOM	CHOP v. third generation regimen
Cooper (51) Full, subgroup	≥60	77	I (bulky), II, III, IV	FLC, DSCC, DM, DLC, IM	CHOP v. MACOP-B	CHOP v. third generation regimen
Gaynor (54)[b] Abstract, subgroup	>60	360	II (bulky), III, IV	FLC, DSCC, DM, DLC, IM, SNCC	CHOP v. m-BACOD v. ProMACE-CytaBOM v. MACOP-B	CHOP v. higher generation regimens
Gordon (55) Full, subgroup	≥60	167	III or IV	DM, DLC, IL	CHOP v. m-BACOD	CHOP v. second generation regimen
Delwail (6) Abstract, primary	76-92	41	III-IV	HG	CVP v. CEP	intravenous v. oral regimen
Jelić (3) Full, primary	>65	47	II-IV	DLC	BEP v. MEP	substitution of mitoxantrone for BCNU
Bastion (12) Full, primary	≥70	453	I(bulky), II, III, IV	FLC, DSCC, DM, DLC, IM, SNCC	CTVP v. CVP	comparing the usefulness of the anthracycline
Bellesi (15) Abstract, primary	≥65	74	NS	DLC, DM, IM, LL, SNCC	MiCEP v. PVABEC	mitoxantrone v. doxorubicin based regimens
Silingardi (18) Full, subgroup	>60	71	IB, II-IV	IG, HG	ProMECE-CytaBOM v. MACOP-B	comparison of third generation regimens
Kitamura (20) Abstract, primary	≥70	316	NS	NS	LD T-COP v. SD T-COP SD T-COP v. HD T-COP	different doses of anthracycline

Note: DLC=diffuse large cell, DM=diffuse mixed, DSCC=diffuse small cleaved cell, FLC=follicular large cell, HD=high dose, HG=high-grade, IG=intermediate grade, IL=immunoblastic lymphoma, IM=immunoblastic, LD=low dose, LL= lymphoblastic lymphoma, NS=not specified, SD=standard dose, SNCC=small non-cleaved cell, v.=versus, WF=Working Formulation.

[a]Please refer to glossary for full names of chemotherapy regimens.

[b]Some data was obtained from Fisher et al. (72).

Table 8. Randomized trials comparing other chemotherapy regimens: results.

Study/Comparison	Results[a]		
	Response rate	Disease control	Overall Survival
Pfreundschuh (10) CHOP v. CHOEP	CR 63.2% v. 69.6% (p=0.055)[b]	NR	NR
Tilly (1) CHOP v. ACVBP	CR 55% v. 55% (p=ns)	EFS (3y) 33% v. 45% (p=0.004) DFS (3y) 50% v. 69% (p=0.0003)	OS (3y) 44% v. 52% (p=0.09)
Tirelli (22) CHOP v. VMP	CR 45% v. 27% (p=0.06) OR 77% v. 50% (p=0.01)	PFS (median)[c] 26m v. 8m (p=0.002)	OS (median)[c] 36m v. 13m (p=0.004); OS (4y) 42% v. 18% (p=0.004)
Montserrat (58) CHOP v. ProMACE-CytaBOM	CR 56.5% v. 54% (p=0.9)[d]	NR	NR
Cooper (51) CHOP v. MACOP-B	CR 67% v. 43% (p=0.04)	FFS 46% v. 45% (p=ns)	OS (4y) 48% v. 49% (p=ns)
Gaynor (54) CHOP v. m-BACOD v. ProMACE-CytaBOM v. MACOP-B	NR	NR	OS (5y) 45% v. 39/41% v. 23% (p=.02)[e]
Gordon (55) CHOP v. m-BACOD	CR 49% v. 62% (p=0.09)[d]	NR	NR
Delwail (6) CVP v. CEP	CR 13% v. 50% (p=0.03)	NR	OS (median) 7 m v. 14 m (p=0.11) OS (2y) 25% (95% CI 6-44) v. 38% (95% CI 17-58)
Jelić (3) BEP v. MEP	CR 30% v. 15% (p=0.68) Overall RR 59% v. 60% (p=0.95)	NR	OS (2y) 30% v. 50% (p=0.6)
Bastion (12) CTVP v. CVP	CR 47% v. 32% (p=0.0001) PR, early death rates identical PD 21% v. 39% (p=0.0001)	TTF (median) 7m v. 5m (p<0.05); TTF (5y) 24% v. 14% (p<0.05)	OS (5y) 27% v. 19% (p<0.05)
Bellesi (15) MiCEP v. PVABEC	CR 46% v. 33% (p =0.34)[d] OR 75% both groups	NR	NR
Silingardi (18) ProMECE-CytaBOM v. MACOP-B	CR 52% v. 68% (p=0.21)	NR	NR
Kitamura (20) LD T-COP v. SD T-COP SD T-COP v. HD T-COP	Overall CR 60% v. 46% (p<0.05) OR 86% v. 83% CR 53% v. 50% (p=ns) OR 79% v. 74% (p=ns)	NR	OS no difference OS Low dose > Standard dose (p=ns)

Note: CR=complete response, CI=confidence interval, DFS= disease-free survival, EFS=event-free survival, FFS=failure-free survival, HD=high dose, LD=low dose, m=months, NR=not reported, ns=not significant, OR=overall response, OS=overall survival, PD=progressive disease, PFS=progression-free survival, PR=partial response, RR=response rate, SD=standard dose, TTF=time-to-treatment failure, v.=versus, y=years.

[a]results shown in same order as chemotherapy regimens presented.

[b]for comparison across all groups.

[c]estimates taken from Kaplan-Meier plots.

[d]Chi-square p-value calculated from data reported.

[e]comparison of CHOP v. ProMACE-CytaBOM or m-BACOD v. MACOP-B (p-value across all groups).

Interpretive summary for this category

Except for one study (3), the studies in this category included patients who did not have any significant comorbid illnesses. In comparison with regimens presumed to be less toxic (e.g., VMP, CVP), anthracycline-containing regimens such as CHOP (22) or CTVP (12) were associated with improvements in OS in patients 70 years of age and older. Two studies (1;10) testing chemotherapy regimens that are more intensive than CHOP both detected an increase in toxicity with no survival benefit detected. Subset analyses comparing CHOP with "second and third generation" regimens (51;54;55;58) show that CHOP is at least as effective or less toxic than these other regimens. The remaining studies (6;15;18;20;56) in this category did not contribute additional information.

Monoclonal Antibodies

One study by GELA (9) evaluated the combination of chemotherapy and monoclonal antibodies. This study scored 2 on the Jadad quality scale, contained adequate information about patient withdrawals, but was not blinded and did not provide the details of the randomization process or concealment. In this trial (9) 399 patients ages 60-80 years were randomized to receive CHOP with or without rituximab 375 mg/m^2 on day 1 of each treatment cycle. Patients randomized to CHOP plus rituximab experienced an improved CR rate (76% v. 63%; p=0.005) and 2-year event-free (57% v. 38%; p<0.001) and overall survival (70% v. 57%; p=0.007). No differences in standardly measured treatment-related toxicity were detected; nine percent of patients receiving rituximab experienced grade 3 or 4 infusion-related toxicities.

Interpretive summary for this category

The administration of rituximab with CHOP improves the response rate and event-free and overall survival compared with CHOP alone and is well tolerated.

Colony Stimulating Factors

Two practice guidelines (34;36) and three RCTs (23;57;59) were identified, which address the growth factors guideline question. One practice guideline (34) has been updated (35;61).

Practice guidelines

Two practice guidelines (34-36;61) address the use of colony stimulating factors in patients receiving myelosuppressive chemotherapy. Based on the results of three randomized trials (62-64), the American Society of Clinical Oncology (ASCO) produced a guideline (34;35) suggesting that primary prophylaxis with colony stimulating factors may reduce the incidence of febrile neutropenia by 50 percent if the incidence of febrile neutropenia is greater than 40 percent in a control population (34). In conjunction with a decision analysis (65) that concludes that primary prophylaxis is cost-effective in this circumstance, the ASCO guideline recommends use of colony stimulating factors when the risk of febrile neutropenia is estimated to be greater than 40 percent. The decision analysis utilized data extracted from a randomized trial assessing primary prophylaxis in patients with small cell lung cancer (62) in which neutropenia was defined as a count of less than 1.0x10^9/L and all patients with febrile neutropenia were treated with intravenous antibiotics in hospital; the perspective taken was that of the hospital-costs payer. The authors do not indicate whether the value of 40 percent applies to the risk to the patient over an entire treatment course or to an individual treatment cycle. The second guideline was published by the Cancer Care Ontario Systemic Treatment DSG (36) and suggests that G-CSF is a reasonable option if quality of life is expected to be improved by a reduction in the number or duration of febrile neutropenic episodes.

Randomized studies

Three randomized studies have evaluated primary prophylaxis with G-CSF in older patients with aggressive histology lymphoma (23;57;59); these trials are detailed in Tables 9 and 10. Two trials scored 2 (23;59) and the third scored 1 (57) on the quality scale. A full paper publication (23) and one abstract (59) contain information on patient withdrawals but not about the method of randomization or concealment. The other abstract (57) lacks details about withdrawals, randomization and concealment.

Table 9. **Trials of colony stimulating factors: patients and therapy.**

Study, publication type and analysis	Patient characteristics				Intervention	
	Age (y)	N	Stage	Pathology	Regimen[a]	Colony stimulating factor
Doorduijn, 2000 (59), abstract,	≥65	408	II-IV	IG/HG	CHOP	G-CSF 300 μg sc day 2-11

primary						
Björkholm, 1999 (57), abstract, primary	≥60	445	II-IV	HG	CHOP or CNOP	G-CSF (5 μg/kg/day) sc day 2-10 or 14 for all cycles
Zinzani, 1997 (23), Full paper, primary	≥60	149	II-IV	DLC, IL, ALCL, PTL	VNCOP-B	G-CSF (5 μg/kg/day) sc day 3 for 5 days

Note: ALCL=anaplastic large cell, DLC=diffuse large cell, HG=high grade, IG-intermediate grade, IL=immunoblastic, PTL=peripheral T-cell, sc=subcutaneously, μg=micrograms, y=years.
[a]Please refer to glossary for full names of chemotherapy regimens.

Table 10. Trials of colony stimulating factors: results.

Study (reference)	Results[a]				
	Chemo delivery	Response rates	Disease control	Survival	Toxicities
Doorduijn, 2000 (59), abstract CHOP/G-CSF	Less delay	CR 53% v. 51% (p=ns)	DFS (3y) 47% v. 43% (p=ns)	OS (3y) 36% v. 40% (p=ns)	Fewer infections, fewer days with fever, fewer days on antibiotics 15.2 v. 8.5 d (p=0.011)
Björkholm, 1999 (57), abstract CHOP or CNOP/G-CSF	NR	CR 52% v. 52% (p=ns)	NR	OS (5y) 54% v. 42%, 24% v. 28% (p=0.39)	Granulocytopenia (WHO grade 4) 62% v. 91% (p<0.001); infections during granulocytopenia requiring hospitalization 32% v. 47% of patients (p<0.001)
Zinzani, 1997 (23), full paper VNCOP-B/G-CSF	NR	CR 60% v. 58% (p=ns) PR 23% v. 22% (p=ns) PD 10.5% v. 13%	RFS (30 m) 76% v. 72% (p=ns)	OS (30 m) 64% v. 62% (p=ns)	Neutrophils (<500/mm^3) 23% v. 55.5% (p=0.00005); clinically relevant infections 5% v. 21% (p=0.004)

Note: CR=complete response, d=day, DFS=disease-free survival, m=months, NR=not reported, OS=overall survival, PR=partial response, PD=progressive disease, ns=not significant, RFS=relapse-free survival, WHO=World Health Organization, v.=versus, y=years.
[a]the order of results as follows: the chemotherapy regimen with colony stimulating factor versus the chemotherapy regimen alone.

Doorduijn et al. (59) randomized 408 patients 65 years of age and older to CHOP with and without G-CSF. No differences were detected in CR rate or three-year DFS or OS. Patients receiving G-CSF experienced fewer WHO grade II-IV infections (p=0.011) and required fewer days of antibiotics (Table 10). The percentage of treatment cycles associated with a WHO grade II–IV infection was 14 (134/949) in patients receiving CHOP alone and 10 (95/926) in patients receiving CHOP plus G-CSF (J.K. Doorduijn, personal communication). While this difference reached statistical significance (p=0.011), the absolute risk reduction of 4 percent corresponds to a number needed to treat (NNT) of 25 cycles in order to prevent one WHO grade II-IV infection. No difference in the percentage of patients experiencing a WHO grade II-IV infection was detected (53% treated with CHOP v. 46% treated with CHOP plus G-CSF; p=0.20). Quality of life was evaluated in this study using the European Quality of Life Questionnaire (EuroQoL), EORTC Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30), and the Multidimensionele Vermoeidheids Index (MVI; a fatigue scale) questionnaires administered after the second, fourth and sixth cycle of treatment and at 3, 6, 10, and 18 months of follow-up (66). Out of the entire group, 162 patients were selected to participate in the quality of life analysis, and 132 agreed to do so, with a 90% questionnaire return rate. No differences in scores between randomized groups were detected.

Using a factorial design, Björkholm et al. (57) randomized 455 patients at least 60 years of age to CHOP or CNOP with and without G-CSF. No differences in CR rate or five-year OS were detected between patients receiving or not receiving G-CSF. Patients receiving G-CSF experienced less WHO grade 4 neutropenia (Table 10) and fewer infections during granulocytopenia (Table 10). Using these data, the patient NNT to prevent one infection during granulocytopenia was six.

Zinzani et al. (23) randomized 149 patients at least 60 years of age to VNCOP-B with or without G-CSF. No statistically significant differences were detected in CR rate (Table 10), partial response

rate (Table 10), relapse-free survival (RFS) at 30 months (Table 10), or OS at 30 months (Table 10). Patients randomized to G-CSF experienced less neutropenia (less than 0.5 x 10^9/L; Table 10) and fewer clinically relevant infections (Table 10). Using these data, the patient NNT to prevent one clinically relevant infection was six. One-third of the patients in the control group who experienced an infection required parenteral antibiotics or hospitalization compared with none in the G-CSF group. The report does not comment on the rate of febrile neutropenia in the control group.

Risk factors for toxicity

The trials testing the role of growth factors failed to detect differences in disease control or survival but did show a reduction in the risk of infections. The Hematology DSG therefore concluded that the ability to make a recommendation regarding the role of primary prophylaxis with growth factors in older patients with aggressive histology lymphoma might be assisted by an evaluation of literature addressing factors that predict for an increased susceptibility to the toxic effects of therapy, including the risk of infection. An evaluation of these prognostic factors is complicated by the inclusion in some studies of an evaluation of factors that predict for other outcome measures, such as OS. Specific multivariable toxicity analyses from two randomized trials (11;12) were reviewed along with an additional six retrospective studies (67-72) dealing with risk factors for toxicity .

Two randomized trials evaluated factors associated with an inferior OS (11;12). In the trial comparing CHOP with CNOP (11), the early toxic death rate was 10 percent for patients receiving CHOP; a multivariate analysis of prognostic factors detected that treatment with CNOP, high lactate dehydrogenase (LDH), bulky disease, and poor performance status (ECOG greater than 1) were associated with a higher risk of death. In the trial comparing CTVP with CVP (12), the group receiving CVTP had a toxic death rate of 15 percent and 13 percent experienced a major infection following the first cycle of therapy; a multivariate analysis detected that advanced stage, performance status, LDH, and albumin were predictive for shorter survival.

Six studies (67-72) have retrospectively evaluated (70;71) factors that predict for treatment toxicity in patients with lymphoma. Only one of these reports was limited to older patients and included a multivariate analysis (67). Gomez et al. (67) evaluated 267 patients 60 years of age and older who received CHOP without growth factors; 53 percent of patients were older than 70 years, 52 percent had stage III or IV disease and 28 percent fell within the high-intermediate or high IPI risk groups. A toxic death was defined as a death occurring within six months of commencing treatment; 13 percent of patients suffered a toxic death with 83 percent of these secondary to infection. Sixty-five percent of the infection-related deaths were associated with neutropenia. A multivariate analysis detected that the only factor that independently predicted for a toxic death was an ECOG performance status of 2 or greater (relative risk 3.5; p=0.000001). Other factors assessed included age, histology, Ann Arbor stage, presence of extranodal disease or B symptoms, disease bulk, IPI risk category, LDH, and doxorubicin dose intensity.

Interpretive summary for this category

Three randomized trials (23;57;59) assessing primary prophylaxis with G-CSF have failed to detect a difference between groups in OS or any measure of treatment efficacy, such as initial response rate or duration of disease control. All three trials, however, did show a reduction in the frequency of severe neutropenia and in the risk of infection. Two studies (23;57) detected that the patient NNT to avoid having one patient experience an infection was six; another study (59) detected that the number of cycles needed to treat to avoid an episode of infection was 25. One study (66) reported quality of life outcomes and failed to detect a difference between randomized groups. Baseline ECOG performance status is the most powerful factor predicting for treatment-related toxicity that results in a toxic death.

V. ONGOING TRIALS

The Hematology DSG is aware of the following ongoing trials:

1. **CRC-TU-NH3003, EU-93028:** Phase III randomized study of CHOP versus MCOP (mitoxantrone) in patients aged 65 years and over with intermediate- or high-grade non-Hodgkin's lymphoma (NHL) (UK).

2. **HOVON-46NHL, HOVON-CKVO-2000-10, EU-20130**: Phase III randomized study of CHOP and filgrastim (G-CSF) with or without rituximab in elderly patients with intermediate- or high-risk non-Hodgkin's lymphoma.

3. **MDA-DM-94017, NCI-T94-0040D:** National Cancer Institute (NCI, USA) sponsored phase III randomized study of sequential treatment with three non-cross-resistant chemotherapy combinations or standard chemotherapy for poor-prognosis intermediate grade and immunoblastic NHL: IDA/CDDP/ARA-C/MePRDL, IDA/VCR/BLEO/CTX/MePRDL, and IFF/DHAD/VP-16 versus standard CHOP. This study will assess the feasibility of delivering full standard doses of chemotherapy to patients over 60 years of age who receive granulocyte-colony stimulating factor support (MD Anderson Cancer Center).

4. **E-4494, CLB-9792, SWOG-E4494:** NCI (USA) sponsored (ECOG, CALGB, SWOG) phase III study of CHOP versus CHOP and Rituximab in older patients with diffuse mixed, diffuse large and immunoblastic large cell histology non-Hodgkin's lymphoma.

5. **CWRU-4496, NCI-G97-1350, AMC-IC-93:** NCI (USA) sponsored phase II study of oral combination chemotherapy and granulocyte-colony stimulating factor in older patients (≥ 60 years) with intermediate- and high-grade non-Hodgkin's lymphoma.

6. **NCI-93-C-0133L, NCI-T93-0023N, NCI-MB-303, CRB-9307:** NCI (USA) phase I/II study of dose-intensive EPOCH with G-CSF in adults with previously untreated bulky stage I and stage II/III/IV aggressive non-Hodgkin's lymphoma.

7. The Sixty Plus Trial from the British National Lymphoma Investigation (http://www.bnli.ucl.ac.uk/uma/version1/clinicians_/60plus.htm) is a randomized phase III trial of PMitCEBO±G-CSF compared to CHOP±G-CSF in patients with bulky stage IA, stages IB-IV, newly diagnosed aggressive histology NHL (excluding Burkitt's, lymphoblastic). Patients 60 years old or greater with no significant comorbid diseases are eligible.

8. Intergruppo Italiano Linfomi randomized phase III study in patients >65 years old of P-VEBEC v. mini-CEOP with G-CSF to be used at the discretion of treating physicians. Patients have advanced stage diffuse large cell lymphoma. Overall interim results have been mentioned in abstract form (73).

9. Italian randomized phase III trial of eight versus 12 week VNCOP-B with G-CSF in older patients with aggressive histology lymphoma (74).

VI. DISEASE SITE GROUP CONSENSUS PROCESS

The Hematology DSG considered the management of older patients with aggressive histology lymphoma to be an important topic for guideline development because of its incidence, the availability of evidence, and a perception that practice patterns varied outside a range suggested by this evidence. The Hematology DSG concluded that treatment of these patients is complex, with the decision-making process requiring knowledge of available evidence and with application of this evidence to each patient after evaluating their specific circumstances, including their preferences. Based on the results of randomized trials that have tested many chemotherapy regimens founded on different principles, the

Hematology DSG concluded that it is possible to provide specific treatment recommendations for older patients who have no significant comorbid health problems or specific preferences that would reduce the priority of providing therapy that offers the best opportunity of durable disease control.

The first topic dealt with the optimum base chemotherapy regimen. The Hematology DSG concluded that CHOP should remain as standard therapy for these patients, just as it currently is for younger patients. The Hematology DSG concluded that age alone should not be the prime determinant for selecting the base chemotherapy regimen but that alternatives to CHOP should be reserved for patients of any age who have significant comorbid conditions or specific preferences. Physicians should be cautioned that many older patients might have significant comorbid illnesses or preferences that would make the use of CHOP inappropriate (75).

The second topic considered dealt with the addition of rituximab to CHOP. The GELA trial testing this agent (9) included patients ages 60 to 80 years with stage II-IV diffuse large B-cell lymphoma, an ECOG performance status of less than 2 and no contraindications to doxorubicin. The Hematology DSG concluded that the reported data were sufficiently strong enough to justify a recommendation stating that these patients should receive rituximab in combination with CHOP. The Hematology DSG also discussed whether this recommendation should be generalized to other patients such as those older than 80 years, with limited stage disease, receiving chemotherapy other than CHOP or receiving subsequent-line chemotherapy. The Hematology DSG concluded that patients older than 80 years who otherwise satisfy criteria for treatment with CHOP do not represent a specific prognostic entity and should, therefore, receive similar treatment to patients aged 60 to 80 years of age. The Hematology DSG concluded that current data are insufficient to support a recommendation to add rituximab to chemotherapy for patients with limited-stage or relapsed disease or for patients receiving chemotherapy other than CHOP.

The third topic considered dealt with the use of growth factors as part of primary therapy in combination with chemotherapy and rituximab. The Hematology DSG initially concluded that in the absence of trials detecting superior disease control, survival, or quality of life, current data were insufficient to support a recommendation to use growth factors as part of primary therapy. The Hematology DSG did conclude that secondary prophylaxis with G-CSF was appropriate and recommended for patients who have experienced a previous episode of neutropenic fever or a treatment delay resulting from prolonged neutropenia. This initial recommendation concerning primary therapy did not achieve unanimous approval from the Hematology DSG—some members regarded a reduction in the risk of infection as a sufficient outcome to justify using G-CSF as primary therapy for all patients. A minority of practitioners from across Ontario who reviewed the initial guideline (August 2000) also supported this position. With the availability of results from three randomized trials indicating that the absolute reduction in infections may be less than initially anticipated (55) and with a review of data that assists in predicting which patients are at greatest risk of life-threatening infections, the Hematology DSG reached consensus for a modified recommendation. The Hematology DSG now concludes that there are insufficient data to support a recommendation to *routinely* use growth factors as part of primary therapy but does support the primary use of growth factors for patients at high risk of developing life-threatening infections. These patients are best identified as those with a poor (ECOG greater than 1) performance status. The Hematology DSG also concluded that this recommendation should be expanded to include those patients who present with neutropenia or who have an active infection at the time that therapy is commenced. The recommendation for using growth factors as part of secondary prophylaxis was not altered.

VII. 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 patients older than age 60 who have newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma, an ECOG performance status of less than 4 and no significant comorbid illnesses.

Draft Recommendations

Key Recommendations

- Combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) is recommended for patients with no apparent cardiac disease or significant comorbidity. Dose and schedule should be the same as that used in younger patients.
- The addition of rituximab to CHOP is recommended for patients with diffuse large B-cell lymphoma.
- There is insufficient evidence to support the routine use of granulocyte-colony stimulating factor as primary therapy.
    - While use of granulocyte-colony stimulating factor shortens the duration of neutropenia and decreases the infection rate in these patients, no differences in disease control or survival have been detected.
    - The primary use of granulocyte-colony stimulating factor is recommended for older patients who are at a particularly high risk of experiencing neutropenic fever. These patients are best identified as those with a poor performance status (ECOG 2 or greater), neutropenia prior to therapy or an ongoing infection; there are insufficient data to recommend the primary use of granulocyte-colony stimulating factor for patients whose sole risk factor is bone marrow involvement with lymphoma.
    - The use of granulocyte-colony stimulating factor as secondary prophylaxis is recommended for patients who have previously experienced an episode of neutropenic fever or a treatment delay resulting from persisting neutropenia.

Qualifying Statements

- Treatment decisions in older patients with aggressive histology lymphoma are complex and may be influenced by comorbidity, patient preferences, quality of life issues and the goals of the treatment program. These factors may alter recommendations for individual patients and require discussion between health care providers, patients and their families.
- Radiation therapy is not considered in this guideline and may be an important part of the treatment plan for these patients.

Related Guidelines

Practice Guidelines Initiative's Practice Guideline Report #12-2: *Use of Granulocyte Colony-Stimulating Factor (G-CSF) in Patients Receiving Myelosuppressive Chemotherapy for the Treatment of Cancer* and 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 110 practitioners in Ontario (49 medical oncologists, 30 hematologists, 21 pharmacists and 10 resident hematologists). The survey consisted of 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. The practitioner feedback was mailed out on August 6, 2002 or October 28, 2002 for staff clinicians and October 10, 2002 for resident hematologists. Follow-

up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Hematology DSG reviewed the results of the survey.

Results

Sixty-four responses (three residents and 61 staff clinicians) were received out of the 110 surveys sent (58% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 53 (three residents and 50 staff clinicians) indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 11.

Table 11. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	51 (96%)[a]	2 (4%)	0
There is a need for a clinical practice guideline on this topic.	52 (98%)[a]	1 (2%)	0
The literature search is relevant and complete.	53 (100%)[a]	0	0
The results of the trials described in the report are interpreted according to my understanding of the data.	50 (98%)[b]	1 (2%)	0
The draft recommendations in this report are clear.	46 (88%)[c]	6 (12%)[d]	0
I agree with the draft recommendations as stated.	46 (88%)[a]	5 (10%)	1 (2%)
This report should be approved as a practice guideline.	46 (88%)[a]	5 (10%)	1 (2%)
	Very likely or likely	**Unsure**	**Not at all likely or unlikely**
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	47 (90%)[a]	4 (8%)	1 (2%)

[a]Three responses were from residents (100% of residents' responses).
[b]Two responses were from residents (100% of residents' responses).
[c]Two responses were from residents (67% of residents' responses).
[d]One response was from a resident (33% of residents' responses).

Summary of Written Comments

Eighteen respondents (34%) provided written comments. The main points contained in the written comments were:

1. Three respondents felt that the conclusions about CHOP plus rituximab (CHOP-rituximab) were premature and required confirmation. One of these respondents felt that the use of CHOP-rituximab should be permissive rather than prescriptive since there are resource utilization issues with CHOP-rituximab.

2. One respondent asked why rituximab use with CHOP was limited to those 60 years of age and older.

3. One respondent felt that the data from the German trial (CHOP-14/21±etoposide) (10) were compelling and that the results were unlikely to change upon publication. The respondent felt that either these results should be incorporated into the conclusions of the guideline or that the guideline's conclusions should be delayed until full paper publication of this study.

4. One respondent commented on the poor quality of the data used to better define the risk factors for toxicity.

5. One respondent requested more guidance on the management of those patients with comorbid illness.

Modifications/Actions

1. The DSG felt that the survival advantage reported with CHOP-rituximab was statistically significant and clinically important, despite the short follow-up. Based on these results, the DSG felt that rituximab should be added to CHOP in this patient population. No changes were made to the recommendations.

2. The DSG has summarized this aspect in the DSG consensus section based on: the lower age limit in the randomized trial, the extension of the treatment principles of those aged 60 to 80 years to those above the age of 80, and the lack of evidence for benefit of CHOP-rituximab, thus far, in younger patients. No changes were made to the recommendations.

3. The DSG concluded that recommendations could be made regarding the use of CHOP- rituximab based on the results of one randomized trial (9) as this trial has been published in full article form and used an intention-to-treat analysis that included all patients. This analysis detected superior overall survival in the group randomized to receive CHOP-rituximab. In contrast, the German study (10) has been published only in abstract form and used a factorial design to assess two questions; the eventual analysis was performed using different methodology. Given this complexity, the DSG concluded that recommendations should not be made until results are published in article form. When published, the results will be incorporated into the guideline. No changes were made to the recommendations.

4. The DSG acknowledges the limited quality of the data available for the assessment of risk factors for toxicity in older patients with lymphoma. However, the DSG felt that the most reasonable interpretation of available evidence, in conjunction with clinical experience, was to recommend that "pre-existing infection" and "neutropenia at the time of commencing chemotherapy" should be included as two risk factors leading to a recommendation to use granulocyte-colony stimulating factor as primary prophylaxis. No changes were made to the recommendations.

5. No evidence exists to better guide therapy for those patients with comorbid illness.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval at the May 2003 teleconference meeting. Twelve of 16 members of the PGCC attended the meeting, and all 12 approved the practice guideline report as written.

The PGCC felt that the guideline covered a lot of questions and the Hematology DSG did a great job handling the questions. One member questioned whether the level of detail was shortchanged given the number of questions and volume of evidence. Other comments included that the guideline was well written overall, the Interpretive Summary was succinct, and 90% practitioner feedback approval indicated great recommendations.

VIII. 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 patients older than age 60 who have newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma, an ECOG performance status of less than 4, and no significant comorbid illnesses.

Recommendations

- Combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) is recommended for patients with no apparent cardiac disease or significant comorbidity. Dose and schedule should be the same as that used in younger patients.
- The addition of rituximab to CHOP is recommended for patients with diffuse large B-cell lymphoma.
- There is insufficient evidence to support the routine use of granulocyte-colony stimulating factor as primary therapy.
  - While use of granulocyte-colony stimulating factor shortens the duration of neutropenia and decreases the infection rate in these patients, no differences in disease control or survival have been detected.
  - The primary use of granulocyte-colony stimulating factor is recommended for older patients who are at a particularly high risk of experiencing neutropenic fever. These patients are best identified as those with a poor performance status (ECOG 2 or greater), neutropenia prior to therapy, or an ongoing infection; there are insufficient data to recommend the primary use of granulocyte-colony stimulating factor for patients whose sole risk factor is bone marrow involvement with lymphoma.
  - The use of granulocyte-colony stimulating factor as secondary prophylaxis is recommended for patients who have previously experienced an episode of neutropenic fever or a treatment delay resulting from persisting neutropenia.

Qualifying Statements

- Treatment decisions in older patients with aggressive histology lymphoma are complex and may be influenced by comorbidity, patient preferences, quality of life issues, and the goals of the treatment program. These factors may alter recommendations for individual patients and require discussion between health care providers, patients and their families.
- Radiation therapy is not considered in this guideline and may be an important part of the treatment plan for these patients.

Related Guidelines

Practice Guidelines Initiative's Practice Guideline Report #12-2: *Use of Granulocyte Colony-Stimulating Factor (G-CSF) in Patients Receiving Myelosuppressive Chemotherapy for the Treatment of Cancer* and Evidence Summary Report #6-8: Rit*uximab in Lymphoma*.

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For a complete list of the Hematology Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit our web site at http://www.ccopebc.ca/.

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APPENDIX I

MEDLINE (1966 to April 1999), CANCERLIT (1983 to February 1999), EMBASE (1980 to January 1999), Current Contents (1993 to May 1999), the Cochrane Library (Issue 2, 1999), and Best Evidence (1991 to August 1999) databases were searched without language restriction. This search was updated in April 2000. The following terms were used for MEDLINE and CANCERLIT: "lymphoma, non-Hodgkin" (MESH, text word), "lymphoma" (text word) combined with "aged" (text word) or "older" (text word) combined with "chemo:" (text word). These terms were then combined with search terms: "practice guidelines" (MESH, text word) or "practice guideline?" (text word) or "guideline?" (text word); "meta-analysis" (MESH, text word) or "meta analy:" (text word) or "metaanaly:" (text word) or "systematic review?" (text word) or "systematic overview?" (text word); "random:" (text word) or "random allocation" (MESH, text word). The CANCERLIT search was limited to non-MEDLINE entries. The following headings were used for EMBASE: "lymphoma" or "non-hodgkin lymphoma"; "age" or "old" or "older"; "chemo*"; "practice guideline?" or "guideline*"; "meta-analysis" or "metaanaly*" or "meta analy*" or "systematic review?" or "systematic overview?"; "random*" or "random allocation?". The Cochrane Library, Current Contents, and Best Evidence were searched using the following terms: "lymphoma" and "older" and "chemotherapy".

The search strategy for the growth factors question used the following terms for MEDLINE and CANCERLIT (limited to non-MEDLINE entries): "lymphoma" (MESH, text word) or "lymphoma, non-hodgkin" (MESH, text word) and "age?" (text word) or "elder:" (text word) or "old:". These terms were then combined with the following terms: "growth factor?" (text word) or "granulocyte-macrophage colony-stimulating factor" (MESH) or "granulocyte colony-stimulating factor" (MESH) and "review?" or "overview" or "guide:". The following terms were used for EMBASE: "lymphoma" and "older" or "aged" and "granulocyte colony stimulating factor" or "granulocyte macrophage colony stimulating factor". Searches of the Cochrane Library, Current Contents, and Best Evidence were performed using the following terms: "lymphoma" and "older" and "colony stimulating factor". The paucity of randomized trials assessing the role of colony stimulating factors in the elderly led to a broadening of the inclusion criteria to include non-randomized studies.

Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-based Series #6-7 Version 2: Section 3

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

The Use of Chemotherapy and Growth Factors in Older Patients with Newly Diagnosed, Advanced-Stage, Aggressive Histology Non-Hodgkin's Lymphoma

T. Kouroukis, N. Ismaila, and the Hematology Cancer Disease Site Group

Review Date: May 24, 2013

The 2003 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2003. In September 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Hematology Cancer Disease Site Group (DSG), endorsed the recommendations found in Section 1 (Clinical Practice Guideline) in May 24, 2013.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

1. What treatment provides the optimum disease control and survival in older patients (at least 60 years of age) with newly diagnosed, advanced-stage, aggressive histology lymphoma?
2. What are the toxicities associated with these treatments?

3. What are the roles of granulocyte-colony stimulating factor or granulocyte macrophage-colony stimulating factor in combination with chemotherapy in these patients?

Literature Search and New Evidence
The new search from October 2001 to January 2013 yielded 19 references representing 17 RCTs (2 RCTs had 2 publications each), evaluating the use of chemotherapy and growth factors in older patients with newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma. Sixteen of these references had full text publications and 3 were in abstract form. There were 3 ongoing studies identified from clinicaltrials.gov. Brief results of these searches are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations
The new data supports existing recommendations. Hence, the Hematology Cancer DSG ENDORSED the 2003 recommendations on the use of chemotherapy and growth factors in older patients with newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma.

Document Review Tool

Number and title of document under review	6-7 The Use of Chemotherapy and Growth Factors in Older Patients with Newly Diagnosed, Advanced-Stage, Aggressive Histology Non-Hodgkin's Lymphoma
Current Report Date	June 2003
Clinical Expert	Dr. Tom Kouroukis
Research Coordinator	Nofisat Ismaila
Assessment Date	1 September 2011
Approval Date and Review Outcome (once completed)	ENDORSED (24 may, 2013)

Original Question(s):

4. What treatment provides the optimum disease control and survival in older patients (at least 60 years of age) with newly diagnosed, advanced-stage, aggressive histology lymphoma?
5. What are the toxicities associated with these treatments?
6. What are the roles of granulocyte-colony stimulating factor or granulocyte macrophage-colony stimulating factor in combination with chemotherapy in these patients?

Target Population:

Patients older than age 60 who have newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma, an Eastern Cooperative Oncology Group (ECOG) performance status of less than 4 and no significant comorbid illnesses

Study Section Criteria:

Inclusion Criteria

1. Fully published reports or published abstracts of randomized controlled trials (RCTs) involving newly diagnosed patients with aggressive histology [intermediate- and high-grade, Working 2 Formulation] lymphoma who were 60 years of age and older.
2. To assess the role of chemotherapy, RCTs must compare at least two chemotherapy regimens.
3. To assess the role of colony stimulating factors, RCTs comparing the use of G-CSF or GM-CSF with a control group were sought.
4. Randomized studies assessing the use of monoclonal antibodies (e.g., rituximab) were eligible.
5. Subgroup analyses based on age or histology were eligible.
6. The outcome measures of interest included at least one of the following: overall survival (OS), disease-free (DFS) or failure-free survival (FFS), time-to-treatment failure (TTF), relapse-free survival (RFS), response rate, toxicity, or quality of life measures.

Exclusion Criteria

Studies were excluded if:

1. Patients included had indolent lymphoma, refractory or relapsed lymphoma, human immunodeficiency virus (HIV) related lymphoma, Hodgkin's disease, multiple myeloma, or other hematological malignancies;
2. Transplantation, maintenance chemotherapy, or interferon were used as interventions; or
3. Radiation therapy was used unevenly in experimental and control groups.
4. Studies assessing the role of chemotherapy were excluded if they incorporated growth factors as part of the primary therapy in all randomized groups.
5. Letters and editorials were not considered.

Search Details:

- October 2001 to January 2013 (Medline January wk 3 and Embase wk 4)
- January 2009 to March 2013 (ASCO Annual Meeting)
- October 2001 to March 2013 (clinicaltrials.gov)

Brief Summary/Discussion of New Evidence:

Of 1587 total hits from Medline and Embase + 35 total hits from ASCO + 75 total hits from clinicaltrials.gov, 19 references representing 17 RCTs (2 RCTs had 2 publications each), were found evaluating the use of chemotherapy and growth factors in older patients with newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma. Sixteen of these references had full text publications and 3 were in abstract form. There were 3 ongoing studies identified from clinicaltrials.gov.

Randomized Control Trials					
Interventions	**Population**	**Follow up**	**Outcomes**	**Brief results**	**References**
R-CHOP Vs. R-FC	Patients with newly diagnosed, histologically confirmed mantle-cell lymphoma, Ann Arbor stage II to IV; ECOG performance status of 2 or less Median age, 70yrs n=560	Median, 37 months	**P:** Rate of complete remission **S:** Overall response rate, the time to treatment failure, overall survival, and toxic effects	• Although complete-remission rates were similar with R-FC and R-CHOP (40% and 34%, respectively; P = 0.10), progressive disease was more frequent with R-FC (14%, vs. 5% with R-CHOP). • Overall survival was significantly shorter with R-FC than with R-CHOP (4-year survival rate, 47% vs. 62%; P = 0.005), and more patients in the R-FC group died during the first remission (10% vs. 4%). • Hematologic toxic effects occurred more frequently in the R-FC group than in the R-CHOP group, but the frequency of grade 3 or 4 infections was balanced (17% and 14%, respectively).	Kluin-Nelemans et al 2012
CHOP Vs. R-CHOP	Patients with untreated DLBCL stage II to IV; ECOG performance status of 2 or less Median age, 69yrs n=399	Total, 10 years	OS and RS	• 252 patients died, 140 (71.1%) in the CHOP arm and 112 (55.4%) in the R-CHOP arm. • The 10-year OS rate for all patients was 35% and the 10-year RS rate was 48%. • The difference between the respective effects of R-CHOP and CHOP on 10-year RS was also significant (56% vs. 38%; P=.0013. • Neither age nor sex had any effect on OS or RS. • The causes of death in the CHOP and R-CHOP arms were lymphoma progression (68% and 56%, respectively), treatment toxicity (11% and 13%, respectively; only 2% of the deaths in each arm were due to infection), cancer other than DLBCL (9% in both arms), other diseases (11% and 21%, respectively) and unknown causes (1 patient and 3 patients, respectively). Most of the other diseases were cardiovascular (10 cases [66%] in the CHOP arm and 16 cases [69%] in the R-CHOP arm).	Mounier et al 2012 and Feugier et al 2005 (GELA–LNH 98-5 trial)
R-CHOP Vs. R-miniCEOP	Patients with untreated DLBCL stage II to IV; ECOG performance status of	Median, 42 months	P: EFS S: RR,OS, RFS and Toxicity	• The rate of complete remission was 70% (p = 0.466). • 5-year EFS rates were 46% and 48% for R-	Merli et al 2012 (ANZINTER3 trial)

	0-3 Median age, 72yrs n=224			miniCEOP and R-CHOP, respectively (p = 0.538). • Patients older than 72 years and with low-risk disease had a better outcome when treated with R-miniCEOP (p = 0.011). • Overall, 76 patients died: 38 in the R-CHOP arm and 38 in the R-miniCEOP arm. • Causes of death were equally distributed between study arms, with the exception of a trend toward a higher number of deaths for lymphoma relapse/progression in the R-miniCEOP group (47% vs. 66% of all deaths, respectively; p = 0.165) • The most frequent event was neutropenia, without differences in the rate of grade III – IV events between the two arms (23%).	
R-CHOP14 Vs. R-CHOP21	Patients with untreated DLBCL stage II to IV Median age, 61yrs n=1080	Median, 37 months	OS, PFS, Toxicity	• Reported grade III/IV toxicities in the R-CHOP21 and R-CHOP14 arms are; neutropenia 57%:31%, thrombocytopenia 5%:9%, Infection 22%:17%, cardiac 1%:2%, nausea and vomiting 8%:8%, mucositis 2%:3%. • A total of 237 deaths and 318 progressions/ relapses/deaths were observed. • Comparison of Kaplan-Meier curves gave a hazard ratio (HR) of 0.96 and p=0.75 for OS and HR=1.0 and p=0.98 for progression-free survival (PFS)	Cunningham et al 2009 & 2011 (Abstract)
R-CHOP14 Vs. R-CHOP21	Patients with untreated DLBCL and aaIPI≥1 Median age, 72yrs n=202	NR	RR, OS, EFS, PFS, Toxicity	• Ninety percent of patients treated with R-CHOP14 received G-CSF, whereas only 66% in R-CHOP21 group. • Response rate (CR+CRu) was 67% in R-CHOP14 arm and 75% in R-CHOP21 arm (p=NS). • The 2-year EFS was 48% in R-CHOP14 arm compared with 61% in R-CHOP21 (p=NS). • A similar trend was observed for 2-year PFS (49% vs 63%), 2-year DFS (57% vs 70%) and 2-year OS (67% vs 70%) (p=NS for all). • Grade 3-4 hematological toxicity was more frequent in R-CHOP14 group, with a higher	Delarue et al 2009 (LNH03-6B GELA Study - Abstract)

				proportion of patients receiving red cell or platelet transfusions and/or experiencing febrile neutropenia, resulting in higher proportion of patients hospitalized for adverse events. In contrast, there was no difference for extra-hematological grade 3-4 toxicities.		
6 x CHOP Vs. 8 x CHOP Vs. 6 x R-CHOP Vs. 8 x R-CHOP	Patients previously untreated, biopsy-confirmed aggressive non-Hodgkin lymphoma of the B-cell type Median age, 68yrs n=1222	Median, 34.5 months	P: EFS S: RR,OS, PFS and Toxicity	• 3-year event-free survival was 47·2% after six cycles of CHOP-14 (95% CI 41·2–53·3), 53·0% (47·0–59·1) after eight cycles of CHOP-14, 66·5% (60·9–72·0) after six cycles of R-CHOP-14, and 63·1% (57·4–68·8) after eight cycles of R-CHOP-14. • Compared with treatment with six cycles of CHOP-14, overall survival improved by –1·7% (–10·0–6·6) after eight cycles of CHOP-14, 10·4% (2·8–18·0) after six cycles of R-CHOP-14, and 4·8% (–3·1–12·7) after eight cycles of R-CHOP-14. • In a multivariate analysis that used six cycles of CHOP-14 without rituximab as the reference, and adjusting for known prognostic factors, all three intensified regimens improved 3-year EFS (eight cycles of CHOP-14: RR [relative risk] 0·76 [0·60–0·95], p=0·0172; six cycles of R-CHOP-14: RR 0·51 [0·40–0·65], p<0·0001; eight cycles of R-CHOP-14: RR 0·54 [0·43–0·69], p<0·0001). • Progression-free survival improved after six cycles of R-CHOP-14 (RR 0·50 [0·38–0·67], p<0·0001), and eight cycles of R-CHOP-14 (RR 0·59 [0·45–0·77], p=0·0001). • OS improved only after six cycles of R-CHOP-14 (RR 0·63 [0·46–0·85], p=0·0031).	Pfreundschuh et al 2008 (RICOVER-60 trial)	
CHOP + Radiotherapy Vs. CHOP alone	Patients with localized stage I or II histologically aggressive lymphoma Median age, 68yrs n=576	Median, 7 years	P: EFS S: RR,OS, and Toxicity	• EFS and OS did not differ between the two treatment groups (P=.6 and P=.5, respectively). • The 5-year estimates of EFS were 61% for patients receiving chemotherapy alone and 64% for patients receiving CHOP plus radiotherapy • The 5-year estimates of OS were 72% and	Bonnet et al 2007	

				68%, respectively. • In a multivariate analysis, OS was affected by stage II disease (P < .001) and male sex (P = .03).		
Mini-CEOP Vs. P-VEBEC	Patients newly diagnosed histologically confirmed DLBCL according to REAL classification, stage II to IV; ECOG performance status of 0-2 Median age, 73yrs n=232	Median, 72 months	OS, Response and Quality of life	• Complete Response (CR) and Overall Response Rates (ORR) were 54% vs 66% (p=0.107) and 90% vs 78% (p=0.021) for P-VEBEC and Mini-CEOP, respectively. • The 5-year OS, Relapse Free Survival (RFS), and Failure Free Survival (FFS) were 32%, 52%, and 21%, respectively. • Subjects achieving a CR showed improvement of QoL regardless of treatment arm.	Merli et al	2007
CHOP Vs. PMitCEBO Vs. CHOP + GCSF Vs. PMitCEBO + GCSF	Patients with previously untreated, bulky stage IA or stages IB-IV aggressive NHL Median age, 70yrs n=784	Median, 44 months	P: FFS S: RR,OS,PFS and Toxicity	• Overall response rate was 84% in the CHOP arm and 83% in the PMitCEBO arm, with overall response rates of 83% for the use of G-CSF and 84% for no G-CSF. • There was no significant difference in failure-free, progression-free or overall survival between the CHOP and PMitCEBO arms. • At 3 years, the actuarial FFS was 44% in CHOP recipients and 42% in PMitCEBO recipients and the 3-year actuarial OS was 46% and 45% respectively. • There was no significant difference in the failure-free, progression-free or overall survival with the addition of G-CS.	Burton et al, 2006	
THP-COP Vs. CHOP Vs. THP-COPE	Patients with previously untreated NHL, disease stage I to IV, performance status of 0 to 3 Median age, 74yrs n=443	Total, 8 years	CR, OS and toxicity	• The complete remission rates for the THP-COP, CHOP, and THP-COPE groups were 42.5%, 41.4%, and 48.0%, respectively. • There was no difference in OS or PFS among these 3 groups. • In aggressive lymphoma, there was also no difference in CR rate (45.3% in THP-COP, 44.9% in CHOP, 48.0% in THP-COPE), OS and PFS among these groups. • The 5- and 8-year survival rates for all patients were 29.4% and 18.7%, respectively. • The 5- and 8-year survival rates for patients	Mori et al	2005

				with aggressive lymphoma were 27.4% and 17.4%, respectively. • In patients with T-cell–type lymphoma, the CR rate was greater after treatment with THP-COP (51.4%) or THP-COPE (57.7%) compared to treatment with CHOP (19.4%).	
MEMID Vs. CEOP	Patients with previously untreated aggressive NHL, Stage II or > Median age, 72yrs n=149	Total, 5 years	P: OS S: RR,EFS and Toxicity	• Neutropenia ($p<10^{-5}$), anemia ($p< 10^{-5}$) and thrombocytopenia (p = 0.0006) were significantly more frequent in patients who received MEMID. • Objective response rate was 55.5% in the MEMID arm and 64.9% in the CEOP arm (p = 0.24). • The median OS and EFS were 15.4 and 8.5 months in the MEMID arm, and 20.3 and 10.5 months in the CEOP arm (p = 0.59 and 0.47), respectively. • The median EFS was 15.4 months in the MEMID arm and 20.3 months in the CEOP arm (p = 0.59)	Chamorey et al 2005
CHOP-21 Vs. CHOP-14 Vs. CHOEP-21 Vs. CHOEP-14	Patients with previously untreated aggressive NHL, Age range,, 61-75yrs n=689	Total, 5 years	P: EFS S: RR,OS, and Toxicity	• Complete remission rates were 60.1% (CHOP-21), 70.0% (CHOEP-21), 76.1% (CHOP-14), and 71.6% (CHOEP-14). • Five-year event-free and OS rates were 32.5% and 40.6%, respectively, for CHOP-21 and 43.8% and 53.3%, respectively, for CHOP-14. • In a multivariate analysis, the relative risk reduction was 0.66 (P= .003) for EFS and 0.58 (P < .001) for OS after CHOP-14 compared with CHOP-21. • Toxicity of CHOP-14 and CHOP-21 was similar, but CHOEP-21 and in particular CHOEP-14 were more toxic	Pfreundschuh et al 2004 (NHL-B2 Trial)
CHOP Vs. MCOP	Patients with previously untreated aggressive NHL, Median age, 74yrs n=155	Median, 51 months	P: Toxicity S: RR,OS	• The median survival was 19 months (95% confidence interval 10–36 months) with an actuarial survival of 47% at 2 years and 42% at 3 years (CHOP versus MCOP, P = 0.79). • There was no significant difference in any of the toxicities experienced with either CHOP or MCOP, except for white cell count (46 patients on MCOP and 27 patients on CHOP	Bessell et al 2003

				had grade 3 or 4 toxicity, P = 0.002) and red cell transfusion (37 patients, MCOP; 17 patients, CHOP; P = 0.001). • Grade 3 or 4 neutropenia was documented in 75 patients (50%). One patient died from toxicity whilst in remission and seven patients died with septicemia and persistent NHL.		
CHOP Vs. CHOP + G-CSF	Patients with previously untreated aggressive NHL, disease stage II-IV, Median age, 72yrs n=389	Median, 33 months	P: CR rate and OS S: EFS, DFS and Toxicity	• The relative dose intensities (RDIs) of cyclophosphamide (median, 96.3% v 93.9%; P = .01) and doxorubicin (median, 95.4% v 93.3%; P = .04) were higher in patients treated with CHOP plus G-CSF. • The complete response rates were 55% and 52% for CHOP and CHOP plus G-CSF, respectively (P = .63). • The actuarial over-all survival at 5 years was 22% with CHOP alone, compared with 24% with CHOP plus G-CSF (P = .76). • Patients treated with CHOP plus G-CSF had an identical incidence of infections, with World Health Organization grade 3 to 4 (34 of 1,191 cycles v 36 of 1,195 cycles). • Only the cumulative days with antibiotics were fewer with CHOP plus G-CSF (median, 0 v 6 days; P =.006) than with CHOP alone. • The number of hospital admissions and the number of days in hospital were not different.	Doorduijn et al 2003	
CHOP Vs. CNOP Vs. CHOP + GCSF Vs. CNOP + GCSF	Patients with previously untreated aggressive NHL, disease stage II-IV, Median age, 71yrs n=455	Median, 57 months	P: TTF S: CR rate, OS, DFS and Toxicity	• The CR rates in the CHOP/CNOP plus G-CSF and CHOP/CNOP groups were the same, 52%, and in the CHOP with or without G-CSF and CNOP with or without G-CSF groups, 60% and 43% (P < .001), respectively. • No benefit of G-CSF in terms of TTF and OS could be shown (P = .96 and P = .22, respectively), whereas CHOP was superior to CNOP (TTF/OS P < .001). • The incidences of severe granulocytopenia (World Health Organization grade IV) and granulocytopenic infections were higher in	Osby et al 2003	

				patients not receiving G-CSF. • The cumulative proportion of patients receiving 90% or more of allocated chemotherapy was higher (P < .05) in patients receiving G-CSF. • Concomitant G-CSF treatment did not improve CR rate, TTF, or OS. • Patients receiving CHOP fared better than those given CNOP chemotherapy.	
Pegfilgrastim Vs. Daily Filgrastim	Patients with NHL requiring treatment with standard CHOP chemotherapy, ECOG status ≤2, Mean age, 70yrs n=27	Total, 3 months	Duration of grade 4 (severe) neutropenia	• Duration of grade 4 neutropenia in cycle 1 was 2.2 (SD 1.2), 1.5 (SD 1.1), 0.8 (1.2) and 5.0 (2.0) days for patients who received pegfilgrastim 60 microg/kg, pegfilgrastim 100 microg/kg, filgrastim 5 microg/kg and no cytokine, respectively. • The baseline characteristics of the pegfilgrastim and filgrastim groups were imbalanced with increased bone-marrow involvement and prior therapy in the former. • When the treatment groups were balanced for these risk factors, duration of grade 4 neutropenia was comparable with 2.0 and 3.0 vs. 0.6 and 0.5 days for pegfilgrastim 100 microg/kg and filgrastim patients with and without these risk factors, respectively. • The incidence of febrile neutropenia (defined as ANC < 0.5 x 10(9)/l and temperature > 38.2degrees C) was low (10% of patients).	Grigg et al 2003
VNCOP-B + G-CSF X 8 weeks Vs. VNCOP-B + G-CSF X 12 weeks	Patients with previously untreated aggressive NHL, disease stage II-IV, Median age, 71yrs n=297	Median, 32 months	OS, RFS, RR, Toxicity	• The CR rates were 63% and 56% in the 8- and 12-week groups. • Relapse-free survival rates were 59% and 55%, respectively. • Hematological and non-hematological toxicities were similar in both treatment groups.	Zinzani et al 2002

Ongoing trials
Retrieved from www.clinicaltrials.gov

Intervention	Official title	Status	Protocol ID	Completion Date	Last updated
4 X R-CHOP-14 Vs. 4 X R-CHLIP-14 Vs. 6 X R-CHOP-14	Improvement of Outcome and Reduction of Toxicity in Elderly Patients With CD20+ Aggressive B-Cell Lymphoma by an Optimised Schedule of the Monoclonal Antibody Rituximab, Substitution of Conventional by Liposomal Vincristine, and	Recruiting	NCT01478542	October 2019	October 16, 2012

Vs. 6 X R-CHLIP-14 Vs. 6 X CHOP-14 Vs. 6 X CHLIP-14	FDG-PET Based Reduction of Therapy.					
R-CVP Vs. R-FC	Purine-Alkylator Combination In Follicular Lymphoma Immuno-Chemotherapy for Older Patients: a Phase III Comparison of First-line R-CVP Versus R-FC (PACIFICO)	Recruiting	NCT01303887	September 2016	May 4, 2011	
2-weekly rituximab Vs. Pharmacokinetic-based dose-dense rituximab	2-Weekly CHOP Chemotherapy With Dose-Dense Rituximab for the Treatment of Patients Aged 61 to 80 Years With Aggressive CD-20 Positive B-Cell Lymphomas: A Phase-II/Pharmacokinetic Study (CHOP-R-ESC)	Recruiting	NCT00290667	December 2013	September 9, 2011	

Abbreviations: R-FC=Rituximab, Fludarabine, And Cyclophosphamide; R-CHOP=Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, And Prednisone; DLBCL=Diffuse Large B-Cell Lymphoma; OS=Overall Survival; RS=Relative Survival; EFS= Event-Free Survival; RR=Response Rate; RFS=Relapse Free Survival; R-miniCEOP=Epirubicin, Cyclophosphamide, Vinblastine, Prednisone and Rituximab; P-VEBEC= Epirubicin, Cyclophosphamide, Etoposide, Vinblastine, Bleomycin, Prednisone; PMitCEBO=Mitoxantrone, Cyclophosphamide, Etoposide, Vincristine, Bleomycin And Prednisolone; GCSF=Granulocyte Colony-Stimulating Factor; FFS=Failure Free Survival; THP=Pirarubicin; COP=Cyclophosphamide, Vincristine, and Prednisolone; E=Etoposide; MEMID=Mitoxantrone, VP16, Methylglyoxal, Ifosfamide and Dexamethasone; CEOP=Cyclophosphamide, Epirubicin, Vincristine and Prednisone; NHL= Non-Hodgkin's Lymphoma; VNCOP-B=Cyclophosphamide, Mitoxantrone, Vincristine, Etoposide, Bleomycin And Prednisone

Clinical Expert Interest Declaration:

Professional Interest, Publication

Instructions. Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

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?	No
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new	a. Yes b. Yes

recommendations are necessary?	
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:	No
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?	Not Applicable

Review Outcome	Endorse
DSG/GDG Approval Date	24 May, 2013
DSG/GDG Commentary	None

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Literature Search Strategy:

Medline

1. meta-Analysis as topic.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]
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 synthes?s 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$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ 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. exp lymphoma, non hodgkin/
43. 41 or 42
44. age?.mp.
45. elder:.mp.
46. old:.mp.
47. 44 or 45 or 46
48. 43 and 47
49. growth factor?.mp.
50. exp granulocyte colony-stimulating factor/
51. exp granulocyte-macrophage colony-stimulating factor/
52. 49 or 50 or 51
53. 48 and 52
54. 40 and 53
55. exp chemotherapy/
56. 48 and 55
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58. 54 or 57
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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.
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6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
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9. or/1-4,8
10. (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.
11. (reference list$ or bibliograph$ 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$3 or dummy)).tw.
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21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
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37. exp lymphoma, non hodgkin/
38. 36 or 37
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41. old:.mp.
42. 39 or 40 or 41
43. 38 and 42
44. growth factor?.mp.
45. exp granulocyte colony-stimulating factor/
46. exp granulocyte-macrophage colony-stimulating factor/
47. 44 or 45 or 46
48. 43 and 47
49. 35 and 48
50. exp chemotherapy/
51. 43 and 50
52. 35 and 51
53. 49 or 52
54. (200202$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$).ew.
55. 53 and 54

ASCO Annual Meeting - searched http://www.ascopubs.org/search with keywords: "Chemoradiotherapy" AND "Non-Hodgkin Lymphoma" AND "Adult" OR "Elderly"

Clinicaltrials.gov - searched http://clinicaltrials.gov/ct2/home with keywords: "Chemoradiotherapy" AND "Non-Hodgkin Lymphoma" AND "Adult" OR "Elderly"

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 phrase "Archived document, not for use in clinical decision making,"

2. **ENDORSED** – An endorsed document is a document that has been reviewed by the DSG/GDG 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.