NCCN Guidelines® Insights

Non-Hodgkin's Lymphomas, Version 1.2013

Featured Updates to the NCCN Guidelines

Andrew D. Zelenetz, MD, PhD¹; William G. Wierda, MD, PhD²; Jeremy S. Abramson, MD³; Ranjana H. Advani, MD⁴; C. Babis Andreadis, MD⁵; Nancy Bartlett, MD⁶; Naresh Bellam, MD, MPH⁷; John C. Byrd, MD⁸; Myron S. Czuczman, MD⁹; Luis E. Fayad, MD²; Martha J. Glenn, MD¹⁰; Jon P. Gockerman, MD¹¹; Leo I. Gordon, MD¹²; Nancy Lee Harris, MD³; Richard T. Hoppe, MD⁴; Steven M. Horwitz, MD¹; Christopher R. Kelsey, MD¹¹; Youn H. Kim, MD⁴; Susan Krivacic, MPAF¹³; Ann S. LaCasce, MD⁴; Auayporn Nademanee, MD¹⁵; Pierluigi Porcu, MD⁸; Oliver Press, MD, PhD¹⁶; Barbara Pro, MD¹⁷; Nishitha Reddy, MD¹⁸; Lubomir Sokol, MD, PhD¹⁹; Lode Swinnen, MB, ChB²⁰; Christina Tsien, MD²¹; Julie M. Vose, MD²²; Joachim Yahalom, MD¹; Nadeem Zafar, MD²³; Mary A. Dwyer, MS²⁴; and Maoko Naganuma, MSc²⁴

Abstract

These NCCN Guidelines Insights summarize several key updates to the NCCN Guidelines for Non-Hodgkin's Lymphomas (NHL) and provide a discussion of the clinical evidence that support the updates. The updates discussed in this article feature recommendations for additional treatment options in patients with chronic lymphocytic leukemia and guidance surrounding the management of hepatitis virus reactivation/infections in high-risk patients with NHL undergoing antitumor therapy. (*JNCCN* 2013;11:257–273)

From ¹Memorial Sloan-Kettering Cancer Center; ²The University of Texas MD Anderson Cancer Center; ³Massachusetts General Hospital Cancer Center; ⁴Stanford Cancer Institute; ⁵UCSF Helen Diller Family Comprehensive Cancer Center; ⁶Site-man Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; ⁷University of Alabama at Birmingham Comprehensive Cancer Center; ⁸The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; ⁹Roswell Park Cancer Institute; ¹⁰Huntsman Cancer Institute at the University of Utah; ¹¹Duke Cancer Institute; ¹²Robert H. Lurie Comprehensive Cancer Center of Northwestern University; ¹³Consultant; ¹⁴Dana-Farber/Brigham and Women's Cancer Center; ¹⁵City of Hope Comprehensive Cancer Center; ¹⁶Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; ¹⁷Fox Chase Cancer Center; ¹⁸Vanderbilt-Ingram Cancer Center; ¹⁹Moffitt Cancer Center; ²⁰The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; ²¹University of Michigan Comprehensive Cancer Center; ²²UNMC Eppley Cancer Center at The Nebraska Medical Center; ²³St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; and ²⁴National Comprehensive Cancer Network.

Disclosures for the NCCN Non-Hodgkin's Lymphomas Panel

Individual disclosures of potential conflicts of interest for the NCCN Non-Hodgkin's Lymphomas Panel can be found on page 258.

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Release date: March 15, 2013; Expiration date: March 15, 2014

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for NHL.
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for NHL.

EDITOR: Kerrin M. Green, MA, Assistant Managing Editor, *JNCCN—Journal of the National Comprehensive Cancer Network*, has disclosed that she has no relevant financial relationships.

CE AUTHORS: Nicole B. Harrold, BS, Manager, Continuing Education and Grants, has disclosed that she has no relevant financial relationships. Kristina M. Gregory, RN, MSN, OCN, Vice President, Clinical Information Operations, has disclosed that she has no relevant financial relationships. James Prazak, RPh, Assistant Director, Continuing Education and Grants, has disclosed the following relationships with commercial interests: Bristol-Myers Squibb Company; Pension; Pfizer, Inc; Stockholder; United Healthcare Group; Stockholder; Johnson & Johnson; Stockholder. Maoko Naganuma, MSc, Oncology Scientist/Senior Medical Writer, has disclosed that she has no relevant financial relationships. Mary A. Dwyer, MS, Guidelines Coordinator, has disclosed that she has no relevant financial relationships.

Disclosure of Affiliations and Significant Relationships: NCCN Non-Hodgkin's Lymphomas Panel

The following authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products or devices discussed in this report or their competitors: Dr. Bellam, Dr. Byrd, Dr. Gockerman, Dr. Harris, Dr. Hoppe, Dr. Kelsey, Dr. LaCasce, Dr. Reddy, Dr. Tsien, Dr. Yahalom, and Dr. Zafar.

The following authors have disclosed that they have financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products or devices discussed in this report or their competitors:

Dr. Zelenetz: Investigator for Abbott Laboratories; Celgene Corporation; Cephalon, Inc.; Millennium Pharmaceuticals, Inc.; Onyx Pharmaceuticals, Inc.; Allos Therapeutics, Inc.; Calistoga Pharmaceuticals; Pharmacyclis, Inc.; Plexikon Inc.; and Seattle Genetics, Inc. PI for Genentech, Inc.; GlaxoSmithKline plc; and Roche Laboratories, Inc. Advisory board member for Abbott Laboratories; Cephalon, Inc.; Genentech, Inc.; GlaxoSmithKline plc; Allos Therapeutics, Inc.; Gilead Sciences, Inc.; Seattle Genetics, Inc.; Roche Laboratories, Inc.; and sanofi-aventis U.S. Consultant for Celgene Corporation; Cell Therapeutics, Inc.; and Cancer Genetics.

Dr. Abramson: Advisory board member for Seattle Genetics, Inc.

Dr. Advani: PI for Genentech, Inc.; GlaxoSmithKline plc; Janssen Pharmaceuticals, Inc.; Allos Therapeutics, Inc.; Seattle Genetics, Inc.; and Pharmacyclis, Inc. Advisory board member for Celgene Corporation; Sanofi Oncology; and Seattle Genetics, Inc.

Dr. Andreadis: Speakers' bureau member for Allos Therapeutics, Inc. Spouse is employed by Roche Laboratories, Inc.

Dr. Bartlett: PI for AstraZeneca Pharmaceuticals LP; Celgene Corporation; Genentech, Inc.; Novartis Pharmaceuticals Corporation; Seattle Genetics, Inc.; Pfizer, Inc.; and Pharmacyclis. Consultant for Seattle Genetics, Inc.

Dr. Czuczman: PI for Celgene Corporation; Cephalon, Inc.; GlaxoSmithKline plc; and Novartis Pharmaceuticals Corporation. Consultant for Celgene Corporation and Millennium Pharmaceuticals, Inc. Advisory board member for Genentech, Inc. and Onyx Pharmaceuticals, Inc.

Dr. Fayad: PI for Centocor, Inc.; Eli Lilly and Company; Genentech, Inc.; Novartis Pharmaceuticals Corporation; Pfizer, Inc.; and Wyeth Pharmaceuticals. Speakers' bureau member for Eisai Inc.; Roche Laboratories, Inc.; and sanofi-aventis U.S.

Dr. Glenn: PI for Piramal Life Sciences and sanofi-aventis U.S.

Dr. Gordon: PI for CureTech Ltd. Speakers' Bureau Member for Genentech, Inc. Advisory board member for CureTech Ltd.

Dr. Horwitz: PI for Celgene Corporation; Allos Therapeutics, Inc.; and Gloucester Pharmaceuticals, Inc. Research support from Millennium Pharmaceuticals, Inc.; Kyowa Hakko Kirin Pharma, Inc.; Seattle Genetics, Inc.; and Spectrum. Consultant for Bristol-Myers Squibb Company; Celgene Corporation; Genzyme Corporation; Merck & Co., Inc.; and Kyowa Hakko Kirin Pharma, Inc. Advisory board member for Allos Therapeutics, Inc. and Seattle Genetics, Inc.

Dr. Kim: PI for Merck & Co., Inc.; Allos Therapeutics, Inc.; Kyowa Hakko Kirin Pharma, Inc.; Seattle Genetics, Inc.; and Yaupon Therapeutics, Inc.

Dr. Krivacic: IRB board member for Janssen Pharmaceuticals, Inc.

Dr. Nademanee: PI for Seattle Genetics, Inc.

Dr. Olsen: PI for Eisai Inc.; Johnson & Johnson Services, Inc.; and Yaupon Therapeutics, Inc. Advisory board member for Merck & Co., Inc.

Dr. Porcu: Advisory board member for Therakos, Inc.

Dr. Press: PI for Genentech, Inc. and Roche Laboratories, Inc. Independent data monitoring committee member for Roche Laboratories, Inc. Consultant for Genentech, Inc. and Roche Laboratories, Inc. Advisory board member for Millennium Pharmaceuticals, Inc.; Onyx Pharmaceuticals, Inc.; Algeta ASA; Allos Therapeutics, Inc.; Seattle Genetics, Inc. Spouse owns stock in Emergent BioSolutions, Inc.

Dr. Sokol: Advisory board member for Alexion Pharmaceuticals, Inc.; Celgene Corporation; Eisai, Inc.; MedImmune, Inc. Speakers' bureau member for Celgene Corporation. Consultant for Allos Therapeutics, Inc.

Dr. Swinnen: Research support from Abbott Laboratories.

Dr. Vose: PI for Bristol-Myers Squibb Company; Celgene Corporation; Genentech, Inc.; GlaxoSmithKline plc; Onyx Pharmaceuticals, Inc.; Incyte Corporation; Biotest Pharmaceuticals Corporation; and Pharmacyclis, Inc.

Dr. Wierda: PI for Abbott Laboratories and GlaxoSmithKline plc.

The NCCN Guidelines Staff have no conflicts to disclose.

Supported by educational grants from Eisai, Inc.; Millennium: The Takeda Oncology Company; Teva Pharmaceuticals; Bayer HealthCare Pharmaceuticals Inc.; Celgene Corporation; Endo Pharmaceuticals and HealthTronics; Genentech; and ARIAD Pharmaceuticals, Inc.

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SUPPORTIVE CARE FOR PATIENTS WITH CLL

Tumor Lysis Syndrome (TLS)	<ul style="list-style-type: none"> Consider tumor prophylaxis measures in patients with bulky disease at high risk for TLS. <ul style="list-style-type: none"> For details on the symptoms, prophylaxis, and management of TLS in NHL, see Supportive Care for NHL (NHODG-B).
Tumor Flare Reactions	<ul style="list-style-type: none"> Management of tumor flare recommended for patients receiving lenalidomide Tumor flare reactions: <ul style="list-style-type: none"> Painful lymph node enlargement or lymph node enlargement with evidence of local inflammation, occurring with treatment initiation; may also be associated with spleen enlargement, low-grade fever, and/or rash Treatment: <ul style="list-style-type: none"> Steroids (eg, prednisone 25-50 mg PO for 5-10 days) Antihistamines for rash and pruritus (cetirizine 10 mg PO QID or loratadine 10 mg PO daily) Prophylaxis: <ul style="list-style-type: none"> Consider in patients with bulky lymph nodes (>5 cm) Steroids (eg, prednisone 20 mg PO for 5-7 days followed by rapid taper over 5-7 days)
Thromboprophylaxis	<ul style="list-style-type: none"> Recommended for prevention of thromboembolic events in patients receiving lenalidomide: <ul style="list-style-type: none"> Aspirin 81 mg daily if platelets above $50 \times 10^{12}/L$ Note that the above may differ from the NCCN Guidelines for Venous Thromboembolic Disease in which the recommendations with lenalidomide pertain only to patients with multiple myeloma

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NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Non-Hodgkin's lymphomas (NHL) represent a highly heterogeneous group of lymphoproliferative disorders, with B-cell lymphomas constituting approximately 80% of NHL cases; 15% to 20% of NHLs are of T-cell origin, whereas natural killer (NK) cell lymphomas are rare.¹ In the United States alone, 69,740 new cases of NHL and 19,020 deaths from NHL are estimated in 2013.² NHL is the seventh leading site of new cancer cases in the United States, accounting for 4% of new cases and 3% of cancer-related deaths.² These estimates do not include cases of chronic lymphocytic leukemia (CLL), which are estimated separately by the American Cancer Society. CLL is the most commonly diagnosed leukemia among adults in the United States, with 15,680 new cases and 4580 deaths estimated for 2013.² The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NHL are continuously updated by a multidisciplinary panel of NHL experts with the

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SUGGESTED TREATMENT REGIMENS^a
(in order of preference)**Frail patient, significant comorbidity
(not able to tolerate purine analogs)**

- Chlorambucil ± rituximab
- Rituximab
- Pulse corticosteroids

See Supportive Care for
Patients with CLL (CSLL-C)

Consider prophylaxis for tumor
lysis syndrome (See NHODG-B)

See monoclonal antibody and
viral reactivation (NHODG-B)

CLL without del (11q) or del (17p)**First-line therapy^b**

- Age ≥70 y or younger patients with comorbidities
 - Chlorambucil ± rituximab
 - Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) ± rituximab
 - Cyclophosphamide, prednisone ± rituximab
 - Alemtuzumab^c
 - Rituximab
 - Fludarabine^{d,e,f} ± rituximab
 - **Lenalidomide^g**
 - Cladribine
- Age <70 y or older patients without significant comorbidities
 - Chemoimmunotherapy
 - ◊ FCR^d (fludarabine, ^fcyclophosphamide, rituximab)
 - ◊ FR^d (fludarabine, ^frituximab)
 - ◊ PCR (pentostatin, cyclophosphamide, rituximab)
 - ◊ Bendamustine ± rituximab

Relapsed/Refractory therapy

See Suggested Regimens for
Relapsed/Refractory therapy for CLL
without del (11q) or del (17p) (2 of 7)

See Suggested Regimens for CLL with del (17p) (3 of 7)

See Suggested Regimens for CLL with del (11q) (4 of 7)

^aSee references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.

^bSee Supportive Care for Patients with CLL (CSLL-C).

^cLess effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

^dAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

^eIn patients ≥70 y, fludarabine does not appear to have a benefit for first-line therapy over other therapies including chlorambucil.

^fSee Discussion for further information on oral fludarabine.

^gLenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.

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aim to put forth timely recommendations on standard practices for diagnostic workup, treatment, and surveillance strategies based on currently available evidence. These NCCN Guidelines Insights summarize several key updates to the NCCN Guidelines for NHL (version 1.2013) and provide a discussion of the clinical data that support the recommendations made by the NCCN NHL Panel (to view the most recent version of these guidelines, visit the NCCN Web site at NCCN.org). The updates discussed include recommendations on treatment regimens for CLL and strategies for surveillance and management of hepatitis virus infections in patients with NHL.

CLL

CLL is characterized by the progressive accumulation of morphologically mature, malignant B lymphocytes in the blood, bone marrow, and lymphoid

tissue. This malignancy primarily affects “elderly” adults, with a median age at diagnosis of 72 years; approximately 70% of patients are diagnosed at older than 65 years of age (and 40% diagnosed at age ≥75 years).³ Important challenges remain in the treatment of this incurable disease, including the need for new agents and regimens to treat elderly or frail patients, and to treat patients with disease resistant to standard therapies because of the presence of poor-risk factors. Although chemoimmunotherapy regimens, such as fludarabine, cyclophosphamide, and rituximab (FCR), represent the standard of care in younger or “fit” patients with CLL,^{4,5} older patients who frequently have comorbidities may not be able to tolerate myelosuppressive regimens.⁶ Moreover, several biological markers have prognostic significance, including in patients treated with chemoimmunotherapy. In the CALGB 9712 trial (N=104) that evaluated first-line therapy with

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SUGGESTED TREATMENT REGIMENS^a

(in order of preference)

CLL without del (11q) or del (17p)

Relapsed/Refractory therapy^b

- Long response^h
 - Retreat as in first-line therapy until short response

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

- Short response^h for age ≥ 70 y (repeating therapy used in immediate prior line not recommended)
 - Chemoimmunotherapy
 - ◊ Reduced-dose FCR^{d,f}
 - ◊ Reduced-dose PCR
 - ◊ Bendamustine $\pm$ rituximab
 - ◊ High-dose methylprednisolone (HDMP) + rituximab
 - Chlorambucil $\pm$ rituximab
 - Ofatumumab
 - **Lenalidomide^g $\pm$ rituximab**
 - Alemtuzumab^c $\pm$ rituximab
 - Dose-dense rituximab (category 2B)

- Short response^h for age < 70 y or older patients without significant comorbidities (repeating therapy used in immediate prior line not recommended)
 - Chemoimmunotherapy
 - ◊ FCR^{d,f}
 - ◊ PCR
 - ◊ Bendamustine $\pm$ rituximab
 - ◊ Fludarabine^{d,f} + alemtuzumab
 - ◊ RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
 - ◊ R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine)
 - ◊ Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab)
 - ◊ OFAR^d (oxaliplatin, fludarabine,^f cytarabine, rituximab)
 - Ofatumumab
 - **Lenalidomide^g $\pm$ rituximab**
 - Alemtuzumab^c $\pm$ rituximab
 - HDMP + rituximab

See Suggested Regimens for CLL with del (17p) (3 of 7)

See Suggested Regimens for CLL with del (11q) (4 of 7)

^aSee references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.

^bSee Supportive Care for Patients with CLL (CSLL-C).

^cLess effective for bulky (> 5 cm) lymphadenopathy; monitor for CMV reactivation.

^dAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

^fSee Discussion for further information on oral fludarabine.

^g**Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment.** See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.

^hLong and short response cannot be rigorously defined based on available data. A major factor is that the definition would be influenced by the prior treatment. Clinicians will need to use clinical judgement. For instance, after a regimen such as FCR, 3 years may be a reasonable cutoff based on the data from MDACC. However, after chlorambucil, 18-24 months may be a reasonable cutoff.

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fludarabine combined with rituximab, the presence of the unmutated *IGHV* gene or poor-risk cytogenetic abnormalities [ie, del(11q) or del(17p)] was associated with significantly decreased progression-free survival (PFS) and overall survival (OS).^{7,8} Unmutated *IGHV* was also associated with significantly decreased time to progression among patients treated with first-line FCR or similar regimens.⁹ In the randomized phase III CLL8 trial (N=817) that compared the FCR regimen with fludarabine combined with cyclophosphamide (FC), treatment with FCR resulted in significantly improved PFS and OS outcomes compared with FC for the subgroups of patients with unmutated *IGHV* or del(11q).⁴ Although FCR was also associated with significantly improved PFS among patients with del(17p), the 3-year PFS rate was only 18%. In addition, 3-year OS outcomes in the subgroup with del(17p) were similar between FCR and FC arms (38% vs. 37%, respectively).⁴ In

a separate analysis from the CLL8 trial, mutation in *TP53* (a tumor suppressor gene located on chromosome 17) was associated with significantly decreased PFS and OS outcomes regardless of treatment with FCR or FC.¹⁰ Given the incurability of CLL with current therapies and the need to improve outcomes for elderly patients or those with poor prognostic features, new regimens and investigational agents are continuously under clinical evaluation.

Lenalidomide in Relapsed/Refractory CLL

Lenalidomide, an immunomodulating agent indicated for the treatment of multiple myeloma and myelodysplastic syndromes, is a thalidomide analog that has shown antitumor activity via its effects on the tumor microenvironment, including inhibition of angiogenesis, modulation of cytokine production, and activation of immune cells.¹¹⁻¹⁶ Initial phase II studies in patients with relapsed/refractory CLL showed that single-agent lenalidomide in-

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SUGGESTED TREATMENT REGIMENS^a

CLL with del (17p)

First-line therapy^b (in order of preference)

- FCR^{d,f}
- FR^{d,f}
- HDMP + rituximab
- Alemtuzumab^c ± rituximab

Relapsed/Refractory therapy^b (in alphabetical order)

- Alemtuzumab^c ± rituximab
- RCHOP
- CFAR^d (cyclophosphamide, fludarabine, ^falemtuzumab, rituximab)
- HDMP ± rituximab
- R-HyperCVAD
- Ofatumumabⁱ
- **Lenalidomide^g ± rituximab**
- OFAR^{d,f}

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 7)

See Suggested Regimens for CLL with del (11q) (4 of 7)

^aSee references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.

^bSee Supportive Care for Patients with CLL (CSLL-C).

^cLess effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

^dAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

^fSee Discussion for further information on oral fludarabine.

^gLenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.

ⁱThis is not effective in patients with lymph nodes >5 cm.

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duced overall response rates (ORR) of 32% to 47% and complete response (CR) rates of 7% to 9%.^{13,17} Among the subgroup of patients with del(11q), the ORR was 39% to 47%, and among the small subgroup of patients with del(17p) it was only 13%.^{13,17} Tumor flare reactions occurred in 58% of patients (grade 3 or 4 in 8%).¹⁷ The most common grade 3 or 4 toxicities included neutropenia (70%), thrombocytopenia (45%), anemia (18%), and febrile neutropenia (15%).¹⁷ Lenalidomide was administered using different dosing schedules in these earlier studies. In one study, patients initially received lenalidomide at the 25-mg-daily dose given intermittently (21 days of a 28-day cycle), which is the dosing schedule used for multiple myeloma. Because of tumor lysis syndrome observed in the first patients on the study, the starting dose was later reduced to 5 mg daily, with subsequent dose escalation up to 25 mg daily.¹⁷ In this study, grade 3 or 4 tumor lysis was reported in 2

patients (5%). In the other study, patients initially received lenalidomide at a dose of 10 mg daily given continuously for 28 days of a 28-day cycle; the dose was escalated up to a maximum of 25 mg daily.¹³ No tumor lysis was reported in this latter study. Studies showed that in patients with CLL, the "standard" 25-mg dose of lenalidomide used in patients with multiple myeloma resulted in excessive toxicity (tumor flare, tumor lysis, and myelosuppression) when given as the initial dose.^{11,17,18}

More recently, lenalidomide was investigated in combination with the anti-CD20 monoclonal antibody rituximab in previously treated patients with CLL. In preclinical studies, lenalidomide was shown to increase the activity of NK cells, which in turn potentially augmented the antibody-dependent cellular cytotoxicity mediated by rituximab.^{15,16} A phase II study evaluated lenalidomide (initial dose of 10 mg/d started on day 9 of cycle 1; given 28 days

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SUGGESTED TREATMENT REGIMENS^a

(in order of preference)

CLL with del (11q)

First-line therapy^b

- Age ≥70 y or younger patients with comorbidities
 - Chlorambucil ± rituximab
 - Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) ± rituximab
 - Cyclophosphamide, prednisone ± rituximab
 - **Lenalidomide^g**
 - Reduced-dose FCR^{d,e,f}
 - Alemtuzumab^c
 - Rituximab
- Age <70 y or older patients without significant comorbidities
 - Chemoimmunotherapy
 - ◊ FCR^{d,f}
 - ◊ Bendamustine ± rituximab
 - ◊ PCR

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 7)

See Suggested Regimens for CLL with del (17p) (3 of 7)

Relapsed/Refractory therapy^b

See Suggested Regimens for Relapsed/Refractory therapy for CLL with del (11q) (5 of 7)

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

^aSee references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.^bSee Supportive Care for Patients with CLL (CSLL-C).^cLess effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.^dAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.^eIn patients ≥70 y, fludarabine does not appear to have a benefit for first-line therapy over other therapies including chlorambucil.^fSee Discussion for further information on oral fludarabine.^gLenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.

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CSLL-D
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of a 28-day cycle) combined with rituximab (375 mg/m² weekly for 4 weeks in cycle 1, then on day 1 of cycles 3–12) in patients with relapsed/refractory CLL (N=59; median 2 prior regimens).^{19,20} The ORR was 66%, with a CR seen in 12% of patients; all CRs were observed after 12 or more cycles of therapy. The median time to treatment failure was 17 months for all patients. The median OS has not been reached, with an estimated 3-year OS rate of 71%. Among the subgroup of patients with del(17p) (n=15), the ORR was 53%, which was not significantly different from the 70% ORR among patients without del(17p). These response rates in the del(17p) subgroup appear promising, and compare favorably to responses reported with lenalidomide alone. However, the subgroup of patients considered fludarabine-refractory (n=12) had a decreased ORR compared with those who were fludarabine-sensitive (33% vs. 70%; P=.04). Moreover, patients with del(17p) who were

also fludarabine-refractory had the worst survival outcomes, with a median OS less than 10 months. The most common grade 3 or 4 toxicities included neutropenia (73%), thrombocytopenia (34%), and infections or febrile episodes (24%). Tumor flare reactions occurred in 27% of patients, but were all grade 1 or 2 events.²⁰

Lenalidomide as First-Line Therapy in CLL

Several studies have also evaluated first-line lenalidomide monotherapy. In a phase II study in patients with previously untreated CLL (N=25), lenalidomide (initial dose of 2.5 mg/d, with dose escalation up to 10 mg/d; given 21 days of 28-day cycle) resulted in an ORR of 56% (all partial responses, no CRs), with a median duration of response of approximately 17 months at a median follow-up of 21 months.¹⁸ Tumor flare reactions (all grade 1 or 2) occurred in 88% of patients. The most common grade 3 or 4 toxicities included neutropenia (72%; grade 4

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SUGGESTED TREATMENT REGIMENS^a

(in order of preference)

CLL with del (11q)

Relapsed/Refractory therapy^b

- Long response^h
 - Retreat as in first-line therapy until short response

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

- Short response^h for age ≥ 70 y (repeating therapy used in immediate prior line not recommended)
 - Chemoimmunotherapy
 - ◊ Reduced-dose FCR^{d,e,f}
 - ◊ Reduced-dose PCR
 - ◊ Bendamustine $\pm$ rituximab
 - ◊ HDMP + rituximab
 - ◊ Chlorambucil $\pm$ rituximab
 - Ofatumumab
 - **Lenalidomide^g $\pm$ rituximab**
 - Alemtuzumab^c $\pm$ rituximab
 - Dose-dense rituximab (category 2B)

- Short response^h for age < 70 y or older patients without significant comorbidities (repeating therapy used in immediate prior line not recommended)
 - Chemoimmunotherapy
 - ◊ FCR^{d,f}
 - ◊ PCR
 - ◊ Bendamustine $\pm$ rituximab
 - ◊ Fludarabine^{d,f} + alemtuzumab
 - ◊ RCHOP
 - ◊ R-HyperCVAD
 - ◊ Dose-adjusted EPOCH-R
 - ◊ OFAR^{d,f}
 - Ofatumumab
 - **Lenalidomide^g $\pm$ rituximab**
 - Alemtuzumab^c $\pm$ rituximab
 - HDMP + rituximab

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 7)

See Suggested Regimens for CLL with del (17p) (3 of 7)

^aSee references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.

^bSee Supportive Care for Patients with CLL (CSLL-C).

^cLess effective for bulky (> 5 cm) lymphadenopathy; monitor for CMV reactivation.

^dAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

^eIn patients ≥ 70 y, fludarabine does not appear to have a benefit for first-line therapy over other therapies including chlorambucil.

^fSee Discussion for further information on oral fludarabine.

^g**Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.**

^hLong and short response cannot be rigorously defined based on available data. A major factor is that the definition would be influenced by the prior treatment. Clinicians will need to use clinical judgement. For instance, after a regimen such as FCR, 3 years may be a reasonable cutoff based on the data from MDACC. However, after chlorambucil, 18-24 months may be a reasonable cutoff.

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CSLL-D
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in 32%), thrombocytopenia (28%; grade 4 in 16%), and anemia (20%; grade 4 in 4%). Grade 3 or 4 infections or febrile events were reported in 36% of patients (grade 4 febrile neutropenia in 8%).¹⁸ After an extended median follow-up of 47 months, 52% of patients remain on therapy.²¹ The 3-year PFS and OS rates were 69% and 85%, respectively. Recurrent myelosuppression was common during long-term treatment.²¹ In another phase II study, lenalidomide (initial dose of 5 mg/d with dose escalation up to 25 mg; given daily for 28 days of 28-day cycle) was evaluated in previously untreated patients aged 65 years or older (N=60; median age, 71 years).²² In this study, the ORR was 65%, with a CR in 10% and an incomplete CR (CRi; CR with residual cytopenias) in an additional 5% of patients. The median time to achieving a CR/CRi was 18 months (range, 9–27 months). After a median follow-up of 31 months, the PFS and OS rates were 60% and 88%, respec-

tively.²² Interestingly, the subgroup of patients with unmutated IGHV (n=33) showed an ORR of 76%, with a CR/CRi rate of 24%. Among the subgroup of patients with del(11q) (n=14), the ORR was 64%, with a CR/CRi rate of 21%. None of the patients with del(17p) experienced a response, and the median PFS in this poor-risk subgroup (n=6) was only 6 months. The most common grade 3 or 4 toxicities included neutropenia (83%; grade 4 in 67%) and thrombocytopenia (47%; grade 4 in 8%). Grade 3 or 4 infections or febrile events were reported in 13% of patients. Tumor flare reactions were common (52%), but were all grade 1 or 2 events.²² An updated analysis from this study reported that 31 patients (52%) experienced responses lasting 36 months or longer; after a median follow-up of 47 months, the median time to treatment failure has not been reached in this subgroup of long-term responders.²³ Lenalidomide seemed to show promising activity in the front-

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SUPPORTIVE CARE FOR NHL

Monoclonal Antibody Therapy and Viral Reactivation

Anti-CD20 Antibody Therapy

Hepatitis B virus (HBV):

- Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (HBcAb) testing for all patients receiving anti-CD20 antibody therapy
 - Quantitative hepatitis B viral load by PCR only if one of the screening tests is positive
 - In areas with high prevalence/population or prevalence is HBV not known, recommend testing all patients receiving immunotherapy, chemotherapy, or chemoimmunotherapy
- Note: Patients receiving IV immunoglobulin (IVIG) may be HBcAb-positive as a consequence of IVIG therapy.
- Prophylactic antiviral therapy is recommended for any patient who is HBsAg-positive and receiving anti-lymphoma therapy. In cases of HBcAb positivity, prophylactic antiviral therapy is preferred; however, if there is a concurrent high-level hepatitis B surface antibody, these patients may be monitored with serial hepatitis B viral load.
 - Avoid lamivudine due to risks of resistance development.
 - Monitor hepatitis B viral load with PCR monthly through treatment and every 3 months thereafter
 - ◊ If viral load is consistently undetectable, treatment is considered prophylactic
 - ◊ If viral load fails to drop, consult hepatologist
 - Maintain prophylaxis up to 12 mo after oncologic treatment ends
 - ◊ Consult with hepatologist for duration of therapy in patient with active HBV

Hepatitis C virus (HCV):

- New evidence from large epidemiology studies, molecular biology research, and clinical observation supports an association of HCV and B-cell NHL. Recently approved direct-acting-antiviral agents (DAA) for chronic carriers of HCV with genotype 1 demonstrated a high rate of sustained viral responses.
 - Low-grade B-cell NHL
 - ◊ According to the American Association for the Study of Liver Diseases, combined therapy with DAA should be considered in asymptomatic patients with HCV genotype 1 since this therapy can result in regression of lymphoma.
 - Aggressive B-cell NHL
 - ◊ Patients should be initially treated with chemoimmunotherapy regimens according to NCCN Guidelines for NHL.
 - ◊ Liver functional tests and serum HCV RNA levels should be closely monitored during and after chemoimmunotherapy for development of hepatotoxicity.
 - ◊ Antiviral therapy should be considered in patients in complete remission after completion of lymphoma therapy.

Anti-CD20 Antibody Therapy and Brentuximab Vedotin

Progressive multifocal leukoencephalopathy (PML):

- Caused by the JC virus and is usually fatal.
 - Diagnosis made by PCR of CSF and in some cases brain biopsy.
- No known effective treatment.
- Clinical indications may include changes in behavior such as confusion, dizziness or loss of balance, difficulty talking or walking, and vision problems.

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NHODG-B
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line setting in CLL, particularly for older patients and those with del(11q).

Preliminary data are available from a study evaluating the combination of lenalidomide with rituximab in previously untreated CLL. In a multicenter phase II study of the CLL Research Consortium, previously untreated patients with CLL (N=69) were treated with lenalidomide (initial dose of 2.5 mg/d, with dose escalation up to 10 mg/d; given 21 days of a 28-day cycle) combined with rituximab (dose escalated to 375 mg/m² cycle 1; 375 mg/m² weekly for 4 weeks in cycle 2, then on day 1 for cycles 3–7).²⁴ Patients in this trial were stratified by age group (age <65 years, n=40; age ≥65 years, n=29). Only 59% of the older patient group completed the planned 7 cycles of therapy compared with 90% of patients younger than 65 years. Tumor flare reactions occurred in 71% of patients, but were grade 1 or 2 in nearly all cases. The most common grade 3 or 4 tox-

icity was neutropenia, which was reported in 49% of patients. Neutropenic fever occurred in 4 patients (6%).²⁴ Among evaluable patients, the ORR in those younger than 65 years (n=35) was 94% (CR in 20%) and the ORR in older patients (n=22) was 77% (CR in 9%). The median PFS in the younger patient group was 19 months after a median follow-up of 17 months. The median PFS in the older patient group has not yet been reached given the short follow-up time; at a median follow-up of 7 months, the estimated PFS rate was 85%.²⁴

Nonhematologic Toxicities With Lenalidomide

In patients with relapsed/refractory CLL treated with single-agent lenalidomide in phase II studies, tumor flare reactions occurred in approximately 30% to 60% of patients.^{13,17} A higher incidence of tumor flare (approximately 50%–90%) was reported in the first-line setting, although these reactions were limited to grade 1 or 2 events.^{18,22} Tumor flare is typically

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observed as painful enlargement of lymph nodes, and may be accompanied by spleen enlargement, low-grade fever, rash, and/or bone pain. Tumor flare reactions were found to be more frequent among patients with enlarged (>5 cm) lymph nodes at baseline.¹³ Tumor lysis syndrome can complicate the treatment of patients with CLL, particularly those with high lymphocyte counts before therapy. In most of the studies with lenalidomide discussed earlier, allopurinol (during cycle 1 or, in one study, during the first 3 cycles) was administered as prophylaxis for tumor lysis.^{17–19,22} Lenalidomide has been associated with increased risk for venous thromboembolism (deep vein thrombosis or pulmonary embolism) in patients with myelodysplastic syndromes or multiple myeloma, particularly when combined with dexamethasone or chemotherapy agents.^{25–30} Published guidelines recommend that patients with multiple myeloma treated with lenalidomide- or thalidomide-containing regimens receive prophylactic aspirin or anticoagulation with low-molecular-weight heparin or warfarin to prevent venous thromboembolism, depending on presence of risk factors.²⁸ Treatment with lenalidomide may also be associated with venous thromboembolic events in patients with CLL,^{13,17,31} but routine prophylactic anticoagulation is currently not indicated.

NCCN Recommendations

The NCCN NHL Panel recommended adding lenalidomide monotherapy as a first-line treatment option for patients without del(17p) or those with del(11q) [but without del(17p)], aged 70 years or older or who are younger with comorbidities (pages 260 and 263 [CSLL-D 1 of 7, and CSLL-D 4 of 7]). This recommendation was based on data from the phase II study of lenalidomide (discussed earlier) in previously untreated elderly patients with CLL. The panel also recommended adding lenalidomide with or without rituximab as a treatment option for relapsed/refractory disease regardless of the presence of del(17p) or del(11q) and regardless of age group (pages 261, 262, and 264 [CSLL-D 2 of 7, CSLL-D 3 of 7, and CSLL-D 5 of 7]). In patients with CLL, lenalidomide should be initiated at a low dose (2.5–5.0 mg), with subsequent dose escalation as tolerated, and may be administered using a continuous or intermittent dose schedule depending on the treatment protocol followed. With continuous dosing, achieving

stable dosing of lenalidomide greater than 10 mg is difficult; a dose of 5 mg daily appears to be needed to achieve responses in a substantial proportion of patients.

For patients who experience tumor flare reactions while treated with lenalidomide-containing regimens, the NCCN NHL Panel recommended the use of steroids to manage lymph node enlargement and inflammation, and antihistamines to manage rash/pruritus (page 259 [CSLL-C 2 of 2]). For patients with bulky (>5 cm) lymph nodes before the start of therapy, tumor flare prophylaxis with steroids may be considered for the first 10 to 14 days of therapy. Severe tumor flare is generally rare if an anti-CD20 monoclonal antibody is initiated at least 1 week before the start of lenalidomide for patients treated with the combination regimen. Routine prophylaxis for venous thromboembolic events is not recommended in patients with CLL undergoing lenalidomide-containing therapies. However, the panel recommended prophylaxis with daily low-dose aspirin in patients with extremely high platelet counts at baseline (page 259 [CSLL-C 2 of 2]).

Supportive Care: Antibody Therapy and Hepatitis Virus Reactivation

Supportive care is a critical component in the overall management of cancer, helping to maximize the benefit of cancer therapy for patients through enhancing tolerability, reducing treatment-related toxicities, and ensuring timely delivery of planned treatment courses. Certain patients with cancer are at increased risk for infectious complications because of profound immunosuppression stemming from myelosuppressive cancer therapy and/or the underlying malignancy. For example, reactivation of latent viruses may occur in the setting of significant immunosuppression in patients with lymphoid malignancies. The NCCN Guidelines for NHL include recommendations for supportive care measures (eg, management of tumor lysis syndrome, infections) in patients undergoing treatment (to view the most recent version, visit NCCN.org). The following section summarizes recommended strategies for surveillance and management of hepatitis virus infections in patients with NHL, particularly those receiving treatment that contains anti-CD20 monoclonal antibodies.

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Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation has been reported in patients treated with chemotherapy with or without immunotherapy agents.^{32–38} HBV carriers with lymphoid malignancies have a high risk of HBV reactivation and disease,³⁹ especially those treated with anti-CD20 monoclonal antibodies (eg, rituximab, ofatumumab).^{40,41} Liver failure and death associated with HBV reactivation have occurred in patients receiving rituximab-containing regimens.^{40,42–45}

Hepatitis B status can be effectively determined by testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb). Given the widespread use of the hepatitis B vaccine, hepatitis B surface antibody (HBsAb) positivity is of limited value; however, in rare cases, HBsAb levels can help guide therapy (see later discussion). Patients with malignancies who test positive for either HBsAg or HBcAb are at risk for HBV reactivation with cytotoxic chemotherapy; approximately 20% to 50% of patients with HBsAg positivity and 3% to 45% with HBcAb positivity develop HBV reactivation.^{32,33,35,38,46–53} False-negative HBsAg results may occur in chronic liver disease; therefore, patients with a history of hepatitis in need of chemotherapy should be assessed through viral load measurement.⁵⁴ HBsAb positivity is generally equated with protective immunity, although reactivated HBV disease may occur in the setting of significant immunosuppression in HBcAb-positive individuals.^{33,55} In patients with B-cell lymphoid malignancies treated with rituximab-containing regimens, HBV reactivation was observed in patients with HBcAb positivity (with or without HBsAb positivity), even among those who were HBsAg-negative before the initiation of treatment.^{35,48,53} A recent meta-analysis and evaluation of FDA safety reports concerning HBV reactivation in patients with lymphoproliferative disorders reported that HBcAb positivity was correlated with increased incidence of rituximab-associated HBV reactivation.⁴⁷ Vaccination against HBV should be strongly considered in HBV-naïve patients (ie, negative for HBsAg, HBsAb, and HBcAb).^{33,56}

Two strategies have been suggested for the clinical management of HBV reactivation in patients with hematologic malignancies undergoing immunosuppressive therapy with monoclonal antibodies. One strategy is to treat patients who are HBsAg-positive or HBcAb-positive with prophylactic antiviral therapy.

As an alternative strategy, close surveillance with a highly sensitive quantitative assay for HBV, combined with preemptive antiviral therapy on a rising HBV DNA load, can be used.³³ Antiviral prophylaxis with lamivudine has been shown to reduce the risks for HBV reactivation in HBsAg-positive patients with hematologic malignancies treated with immunosuppressive cytotoxic agents.^{39,57–60} A small randomized study in HBsAg-positive patients with lymphoma (N=30) showed that antiviral prophylaxis with lamivudine was superior to deferred preemptive therapy (ie, antivirals given at the time of serologic evidence of HBV reactivation based on viral DNA in serum samples).⁵⁷ HBV reactivation occurred in 53% of patients in the deferred therapy arm compared with none in the prophylaxis arm. In a meta-analysis of clinical trials evaluating the benefit of lamivudine prophylaxis in HBsAg-positive patients with lymphoma treated with immunosuppressive regimens, prophylaxis resulted in significant reductions in HBV reactivation (risk ratio, 0.21; 95% CI, 0.13–0.35) and a trend toward reduced HBV-related deaths (risk ratio, 0.68; 95% CI, 0.19–2.49) compared with no prophylaxis.⁶⁰ Surveillance and antiviral prophylaxis (or preemptive therapy) should be continued for at least 6 to 12 months after the last dose of therapy.³³

The optimal antiviral strategy remains unclear. Although prophylaxis with lamivudine has been evaluated in the setting of immunosuppressive antitumor therapy, development of resistance to lamivudine can be a concern.^{61–65} Adefovir has been evaluated in combination with lamivudine in patients with lamivudine-resistant HBV infections.^{66,67} Tenofovir has shown superior antiviral efficacy compared with adefovir in phase III randomized double-blind studies in patients with chronic HBV infection, and may be the preferred agent in this setting⁶⁸; however, limited data are available regarding its use in patients with cancer. Entecavir and telbivudine have also been evaluated in patients with chronic HBV infection in randomized open-label studies, with adefovir as the comparator, and both agents have shown improved antiviral activity compared with adefovir.^{69,70}

NCCN Recommendations

The panel recommended HBsAg and HBcAb testing for all patients planned for treatment with anti-CD20 monoclonal antibody-containing regimens (page 265 [NHODG-B 2 of 3]). In individuals who test positive for HBsAg and/or HBcAb, a baseline

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quantitative polymerase chain reaction (PCR) for HBV DNA should be obtained to determine viral load. However, a negative baseline PCR does not preclude the possibility of reactivation. In patients from areas with high HBV prevalence (Asia, Africa, Eastern Europe, and portions of South America) or regions where the prevalence is not known, all patients undergoing immunotherapy, chemotherapy, or chemoimmunotherapy should be tested for HBsAg and HBcAb. Patients receiving intravenous immunoglobulin (IVIG) may be HBcAb-positive as a consequence of IVIG therapy, although HBV viral load monitoring is recommended.⁷¹ Prophylactic antiviral therapy is recommended for patients who are HBsAg-positive and undergoing antitumor therapy. For patients who are HBsAg-negative but HBcAb-positive, antiviral prophylaxis is also the preferred approach; however, if these patients concurrently have high levels of HBsAb, they may be monitored with serial measurements of HBV viral load and treated with preemptive antivirals on increasing viral load. During the treatment period, viral load should be monitored monthly with PCR and then every 3 months after completion of treatment. If viral load is consistently undetectable, prophylaxis with antivirals should be continued. If viral load fails to decrease, consultation with a hepatologist is recommended. Several options exist for antiviral agents for prophylactic measures. The optimal choice will be determined by institutional standards or recommendation from hepatology or infectious disease consult. The appropriate duration of prophylaxis remains undefined, but the panel recommended that prophylactic antivirals be maintained for up to 12 months after the completion of antitumor therapy (page 265 [NHODG-B 2 of 3]).

Hepatitis C Virus–Associated B-Cell NHL

Case-control studies have shown a strong association between seropositivity for hepatitis C virus (HCV) and development of NHL, particularly for B-cell lymphomas.^{72–80} In large population-based or multicenter case-control studies, prevalence of HCV seropositivity was consistently increased among patients with B-cell histologies, including diffuse large B-cell lymphoma (DLBCL) and marginal zone lymphomas.^{74,75,78,80} A retrospective study in patients with HCV infection (N=3209) showed that the cumulative incidence of

developing malignant lymphomas was significantly higher among patients with persistent HCV infection compared with those who had sustained virologic response (SVR) to interferon-containing therapy (15-year incidence rate, 2.6% vs. 0%; $P=.016$).⁸¹ Moreover, based on multivariate analysis, persistent HCV infection remained a significant independent factor associated with development of malignant lymphomas (hazard ratio, 7.49; $P=.049$). This study suggested that achievement of SVR with interferon-based therapy may reduce the incidence of malignant lymphoma in patients with HCV infection.⁸¹

HCV as a Target for Treatment of Indolent NHL

Several published reports suggested that treatment with antivirals (typically interferon with or without ribavirin) led to regression of NHLs in HCV-positive patients,^{82–87} providing additional evidence for the potential pathogenic role of HCV infection in the development of lymphoproliferative diseases. In a multicenter retrospective study from a large series of HCV-positive patients with indolent NHL, antiviral therapy (interferon or pegylated interferon, with or without ribavirin) resulted in SVR in 78% of patients who received antivirals in first-line ($n=76$) and in 56% of those who received antivirals as second-line therapy after failure of initial treatment ($n=18$).⁸² Patients in this analysis did not require immediate treatment for their lymphoma. The overall hematologic response was 78% among both subgroups treated with antivirals in first-line (CR in 47%) and second-line therapy (CR in 27%). In the group of patients who received antivirals in the first line, hematologic response was significantly associated with achievement of SVR.⁸² Thus, in HCV-positive patients with indolent NHL not requiring immediate antitumor therapy with chemoimmunotherapy regimens, initial treatment with interferon (with or without ribavirin) seemed to induce lymphoma regression in a high proportion of patients.

In HCV-positive patients with NHL who experience a remission with antitumor therapy, subsequent treatment with antivirals may be associated with lower risk of disease relapse. In a retrospective study of patients with NHL (N=343; indolent and aggressive histologies) who experienced a CR after chemotherapy, the subgroup of HCV-positive patients treated with antivirals (interferon and ribavirin; $n=25$) had significantly longer disease-free survival compared with HCV-positive patients who did not

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receive antiviral therapy (n=44); the probability of relapse-free survival rates at 5-year follow-up were 76% and 55%, respectively.⁸⁸ In addition, none of the patients with an SVR to antivirals (n=0 of 8) experienced relapse, compared with 29% who did not experience response to antivirals (n=5 of 17).

HCV Infection Complicating NHL Therapy

The optimal management of HCV-positive patients with NHL remains to be defined. Patients with indolent NHL and HCV seropositivity may benefit from antiviral treatment as initial therapy, as demonstrated in several reports.^{82,84,86,87,89} In patients with aggressive NHL, an earlier analysis of pooled data from Groupe d'Etude des Lymphomes de l'Adulte (GELA) clinical studies (before the rituximab era) suggested that HCV seropositivity in patients with DLBCL was associated with significantly decreased survival outcomes, partly because of severe hepatotoxicity among those with HCV infection.⁹⁰ Subsequent studies in the chemoimmunotherapy era with rituximab showed that HCV seropositivity was not predictive of outcomes in terms of PFS or OS in patients with DLBCL.^{91,92} However, the incidence of hepatotoxicity with chemoimmunotherapy was higher among HCV-positive patients, confirming the observation made in the GELA studies.

The treatment of chronic HCV infection has improved with the advent of newer antiviral agents, especially those that target carriers of HCV genotype 1. Direct-acting antiviral agents (DAAs) administered in combination with standard antivirals (pegylated interferon and ribavirin) have shown significantly higher rates of SVR compared with standard therapy alone in chronic carriers of HCV genotype 1.^{93–96} Telaprevir and boceprevir are DAAs that were recently approved by the FDA for the treatment (in combination with pegylated interferon and ribavirin) of patients with HCV genotype 1 infection. The updated guidelines for the management of HCV infection from the American Association for the Study of Liver Diseases (AASLD) recommended that DAAs be incorporated into standard antiviral therapy for patients infected with HCV genotype 1.⁹⁷

NCCN Recommendations

For HCV-positive patients with low-grade B-cell NHL, the panel recommended initial antiviral therapy in asymptomatic patients. For those with HCV genotype 1, triple antiviral therapy with inclusion of

DAAs should be considered as per AASLD guidelines (page 265 [NHODG-B 2 of 3]). HCV-positive patients with aggressive B-cell NHL should initially be treated with appropriate chemoimmunotherapy regimens according to the NCCN Guidelines for NHL (to view the most recent version of these guidelines, visit NCCN.org). Liver function and serum HCV RNA levels should be closely monitored during and after chemoimmunotherapy for the development of hepatotoxicity (page 265 [NHODG-B 2 of 3]). Antiviral therapy should then be considered in patients who experience a CR after the completion of chemoimmunotherapy.

Conclusions

These NCCN Guidelines Insights for NHL highlight key updates to the management of patients with CLL, with a focus on the addition of lenalidomide-containing therapy as a treatment option. Although these NCCN Guidelines updates are derived from evaluation of the most current available evidence at the time of the annual panel meetings, the NCCN NHL Panel recognizes that guidelines updates are an iterative process because of the rapidly evolving field of cancer research. To provide optimal disease management strategies for each patient, physicians must use their clinical judgment when interpreting the recommendations put forth in the guidelines. The NHL panel continues to emphasize the importance of participation in prospective clinical trials when possible and appropriate for the patient. The management of infectious complications is an important supportive care measure for patients with NHL undergoing potentially myelosuppressive antitumor regimens.

These NCCN Guidelines Insights highlight recommendations for surveillance and management of hepatitis virus reactivations and hepatitis infections in high-risk patients with B-cell NHL. The approach to monitoring and managing infectious events should be individualized based on a patient's unique set of clinical circumstances that define the risk for infections. In addition to management of infection, other supportive care considerations must be integrated into the overall continuum of care in the treatment of patients with NHL. Clinicians are encouraged to consult the full version of the 2013 NCCN Guidelines for NHL, including the sections on CLL and

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Supportive Care (to view the most recent version of these guidelines, visit NCCN.org).

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Posttest Questions

1. True or False: The management of infectious complications is an important supportive care measure for patients with NHL undergoing potentially myelosuppressive antitumor regimens.
2. True or False: The approach to monitoring and managing infectious events should be individualized based on a pa-

tient's unique set of clinical circumstances that define the risk for infections.

3. True or False: For HCV-positive patients with low-grade B-cell NHL, the panel recommended initial antiviral therapy in asymptomatic patients.

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JNCCN-N-0178-0313