and a new response category, Indeterminate Response (IR).[1] The IR category can be applied in one or more situations[1]: ≥50% increase in SPD *without* clinical deterioration[2]; appearance of new lesions or increase in size (≥50% PD) of one or more lesions not sufficient to meet criterion 1[3]; and increase of PET uptake in ≥1 lesion. Crucial to the correct use of the IR category is the ancillary use of additional biopsies and mandatory reimaging after 12 weeks. Also, at the time of next reimaging, one must compare the images obtained at the time of initial IR1 with those obtained 12 weeks later. Further "progression" exceeding a 10% increase in SPD documents indicates genuine progressive disease. This use of LYRIC is considered *provisional* and will obviously need reassessment as more experience is acquired.

Will this new response assessment process work? Will it provide accurate evaluation of new therapeutic agents? Will it be safe for patients to continue treatment with agents that would have been stopped using traditional response criteria? Will regulatory agencies accept response assessments based on criteria including the new category IR? These major questions will only be answered if the research community applies these new criteria with consistency and the observed results are widely shared and constructively criticized. Particularly challenging will be the necessity to avoid the mistake of considering a new agent ineffective while at the same time protecting patients from continuing to be exposed to worsening toxicity because off-target tissue injury is erroneously considered nonspecific. It is imperative that we all remember the *provisional* nature of these proposed changes and actively participate in their refinement. Our research community is indebted to Cheson and his coauthors for their willingness to tackle these challenging questions and to provide us with a workable set of guidelines to improve and validate lymphoid cancer response assessment.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. *Blood*. 2016; 128(21):2489-2496.

2. Cheson BD, Horning SJ, Coiffier B, et al; NCI Sponsored International Working Group. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. *J Clin Oncol*. 1999;17(4):1244-1253.

3. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol*. 2014;32(27):3048-3058.

4. Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. *Ann Oncol*. 2011;22(7):1622-1627.

5. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369(1):32-42.

6. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2013;369(6):507-516.

7. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia. *Blood*. 2014;123(22):3390-3397.

8. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372(4):311-319.

9. Cheson BD, Pfistner B, Juweid ME, et al; International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579-586.

10. Cheson BD, Fisher RI, Barrington SF, et al; Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphorra Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.

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● ● ● LYMPHOID NEOPLASIA

Comment on Arcaini et al, page 2527

Novel antivirals for HCV-associated lymphomas

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In this issue of *Blood*, Arcaini et al have identified that patients with indolent B-cell non-Hodgkin lymphomas (NHLs) associated with chronic hepatitis C virus (HCV) infection, particularly those with marginal zone lymphomas (MZLs), can achieve both virologic and lymphoma responses when treated with highly effective, novel HCV eradication therapy.[1]

A strong association between HCV and certain NHLs, including a possible etiologic link, had been previously reported in studies showing that effective eradication of HCV with traditional interferon (IFN)–based therapy was strongly associated with NHL regression in most patients.[2-5] However, IFN-based therapies are long and toxic, and achieve sustained HCV eradication in about 60% to 80% patients.[2,3]

Over the last decade, several novel direct-acting antivirals (DAAs) against HCV have been developed. These agents target structural and nonstructural proteins involved in HCV RNA replication and virus assembly inside infected hepatocytes. DAAs can be given alone or in combination with IFN/ribavirin or other DAAs that inhibit additional regions of the HCV genome, in order to reduce the emergence of resistant variants. DAA-containing regimens are highly effective, as measured by sustained virologic responses in as high as 90% of treated patients. In addition to greater efficacy, these regimens are significantly less toxic than traditional IFN-containing regimens.[6-8] Therefore, it makes sense to investigate whether the use of DAAs in the treatment of HCV-associated B-cell NHL may improve lymphoma response rates and outcomes with less toxicity.

In the present study, Arcaini and colleagues assembled a cohort of 46 patients with indolent B-cell NHL and simultaneous hepatitis C infection who were treated with DAAs at various centers in Europe and 1 center in the United States. Antiviral therapy was given with the goal of eradicating the hepatitis C infection while simultaneously attempting to treat the lymphoma. Because the study was not prospective, patients received different

types of DAA-based regimens, most commonly including sofosbuvir.

As anticipated, DAA induced sustained virologic responses at 12 weeks in all but 1 patient, with very little reported toxicity. With a median follow-up of only 8 months (range, 2-30 months), and a median duration of DAAs of 12 weeks (range, 6-24 weeks), all patients received the entire intended course of antiviral therapy with the exception of 1 patient with advanced cirrhosis who had NHL progression on DAAs.

In terms of lymphoma responses, ~2 of 3 patients responded to DAAs. One of the most interesting findings of this study is that 11 of 12 complete responses occurred in patients with MZL, whereas there were no responses in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. This suggests that the biology of the NHL and its interaction with chronic HCV infection play an important role in lymphomagenesis and therapeutics. It also cautions that effective HCV eradication may not necessarily treat non-MZL histologies, and that these patients may still require standard therapies such as chemoimmunotherapy. However, there were only 9 patients with non-MZL histologies, and this observation will require further prospective investigation.

In the entire study cohort, 12 patients had received prior IFN-based HCV therapy, and 10 patients had received prior systemic therapy for indolent NHL. Neither of these factors was associated with a lack of response to DAAs, strengthening the idea that cessation of chronic HCV antigenic stimulation is the key biologic event leading to lymphoma regression. This important assumption has therapeutic implications: HCV therapy appears to be effective as lymphoma therapy whether it is used in the first line or relapsed settings. HCV therapy makes most sense in patients with indolent NHL who do not have an immediate need for systemic therapy, and who can safely wait several weeks for the immunologic effects of DAAs to take place. At the same time, HCV therapy may also be equally appropriate following standard chemoimmunotherapy for advanced, symptomatic NHL.

Within the short length of follow-up, 6 patients experienced lymphoma progression (1 during DAA, 5 after DAA), all with MZL. It is possible that their lymphomas progressed because the initial virologic response was not sustained; however, this information is not available. It is also possible that successful HCV eradication did not sufficiently reverse the complex immunologic processes that gave rise to the NHL, particularly in the patients whose MZL progressed within 3 months of DAAs. The latter hypothesis is consistent with the observation that in other NHLs associated with chronic infections such as gastric and ocular adnexal MZL, eradication of the putative microorganism does not consistently eradicate the lymphoma.

Although the data presented by Arcaini and colleagues advance our understanding of the relationship between HCV infection, HCV therapy, and B-cell NHL, there are a number of outstanding issues. First, longer follow-up is required to determine whether sustained virologic responses and their ensuing sustained lymphoma responses will translate into favorable long-term outcomes for these patients. Second, prospective studies involving homogeneous treatments and assessments, together with biologic correlates, are necessary to identify the most effective strategy for the subgroup of patients most likely to benefit. Third, pharmacoeconomic analyses should be built into these studies because DAA-based therapy is expected to incur a significant economic burden for the payer, public or private, responsible for the cost of HCV therapy. However, this may turn out to be a cost-effective investment in the long run if these 2 chronic diseases are simultaneously successfully managed and even possibly cured.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Arcaini L, Besson C, Frigeni M, et al. Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. *Blood*. 2016; 128(21):2527-2532.

2. Arcaini L, Vallisa D, Rattotti S, et al. Antiviral treatment in patients with indolent B-cell lymphomas associated with HCV infection: a study of the Fondazione Italiana Linfomi. *Ann Oncol*. 2014;25(7):1404-1410.

3. Michot JM, Canioni D, Driss H, et al; ANRS HC-13 Lympho-C Study GroupAntiviral therapy is associated with a better survival in patients with hepatitis C virus and B-cell non-Hodgkin lymphomas, ANRS HC-13 lympho-C study. *Am J Hematol*. 2015;90(3):197-203.

4. Vallisa D, Bernuzzi P, Arcaini L, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. *J Clin Oncol*. 2005;23(3):468-473.

5. Hermine O, Lefrère F, Bronowicki JP, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. *N Engl J Med*. 2002;347(2):89-94.

6. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013;368(20):1878-1887.

7. Jacobson IM, Gordon SC, Kowdley KV, et al; POSITRON Study; FUSION Study. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013;368(20):1867-1877.

8. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med*. 2013;368(1):34-44.

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● ● ● RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Urrutia et al, page 2550

Pericytes: new EPO-producing cells in the brain

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In this issue of *Blood*, Urrutia et al identified pericyte as a novel erythropoietin (EPO)-producing cell type in the brain. The brain pericytes function as oxygen sensors and respond to hypoxia. They are regulated by hypoxia-inducible factor (HIF)-2 and prolyl-4-hydroxylase (PHD) 2 and 3.[1]

EPO is the principle cytokine for the production of red blood cells, especially under hypoxic conditions. During mammalian fetal developmental, EPO is mainly generated in the liver, which is also one of the major organs for fetal erythropoiesis. After birth, the majority of EPO is produced in the kidneys. Main renal EPO-producing cells (EPCs) are peritubular interstitial cells that express markers