of a unique antigen-driven pathologic process. This finding again supports the possibility that the NHL originated from a B-cell clone that was already present and antigenically stimulated at the time of MC onset.

We agree that a formal demonstration of the identity of HCV-associated NHLs with B-cell clone(s) that produce RFs could be derived only by a direct comparison of the amino acid (AA)–deduced sequence of the IgR expressed by the lymphomatous clone with the AA sequence of the specific RFs present in the sera of each single patient. But this was beyond the scope of our study. Nevertheless, it is our intent to prove this point by comparing the AA-deduced Ig sequence obtained from serum of some of these patients with their NHL IgR sequence.

Concerning the suggested implication of HCV as the pathogenic agent of the HCV-associated NHLs, this was derived from the analysis of sequence homologies between the IgR expressed by the NHLs and that of antibodies specific for the E2 protein of HCV. In our opinion, such a hypothesis is interesting in the light of the almost complete association and supposed pathogenic relationship between HCV infection and MC syndrome, which precedes NHL onset, at least in a large group of NHL patients. Although such a hypothesis needs a formal demonstration, it is worth noting that Chan et al have recently reported that HCV-associated NHLs and normal B cells responding to E2 viral antigen preferentially use the VHI-69 gene, which is also used by some NHLs we analyzed (VHI-69 is synonymous with VHI/DPI0 and VHI/DPI-I0 and VHI/DPI-88 genes differ in only 1 nucleotide) and is typically used by RF-WAs present in MC. Thus these data indicate that some RF-WAs may have an anti-HCV specificity. Moreover, in HCV infection the reactivity of IgM with the corresponding IgG is inhibited by the addition of HCV antigens, suggesting that the antigen-binding site of the IgM is cross-reactive with HCV antigens. Furthermore, IgG-IgM WA immune complexes were found in HCV-infected patients but not in acute and chronic hepatitis B and acute hepatitis A infections. Thus IgG-IgM WA immune complexes appear to be uniquely associated with HCV infection, supporting the possibility that they derive from an antigen-driven response closely related to the virus.

Finally, since antibody specificity is primarily dependent on the CDR3 region, which is the most variable part of the V region, we have limited the search for sequence homologies to this part of the IgR region. But the results of database research using the entire AA-deduced V sequence again confirms significant homologies with some RFs in most of the cases. Concerning the IgR sequence reported for patient 13, we agree that it may not be similar to that of RF-Bor (the E value was high). In contrast, the homology reported for patient 14 with RF is valid, RF-MR20 being a human rheumatoid factor.

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References

To the editor:

Clarifications to the standard neutrophil response criteria for clinical trials in myelodysplastic syndromes are needed

The recent article by Cheson et al represents an important step toward standardizing the response criteria used in clinical trials of new therapeutic agents for patients with myelodysplastic syndromes (MDSs). We believe that 3 clarifications are necessary to the proposed neutrophil response criteria to avoid classifying patients with spurious increases in neutrophil count as having responded to therapy and to appropriately classify patients who enjoy a genuine, physiologically relevant increase in neutrophil count.

The international working group’s proposed criteria for the increment in peripheral blood counts necessary to qualify as a minor erythroid response and minor platelet response incorporate minimum absolute increments of 1 g/dL and 10 000/mm³ (for transfusion-independent patients), respectively. The proposed minor neutrophil response criterion, in contrast, does not incorporate a minimum absolute increment but simply requires an increase in the absolute neutrophil count (ANC) of at least 100%, but absolute increase less than 500/mm³.

For patients with very low neutrophil counts, the lack of an absolute minimum increment required in order to meet the minor criterion may be problematic. Many factors contribute to day-to-day variability in the neutrophil count in normal persons, and we have also observed such day-to-day variability in patients with MDS in the absence of any specific intervention directed at the neutrophil cell line. The time of day at which blood is drawn for analysis, the degree of recent physical exertion, and (for premenopausal women) the phase of the patient in the menstrual cycle are just some of the many factors that can contribute to daily variability in ANC. The precision and accuracy of laboratory determinations of the ANC in patients with very low neutrophil counts may also be questionable. A hypothetical patient with MDS who began a clinical trial with an ANC of 100/mm³ and subsequently was found to have an ANC of 200/mm³ could be listed as a minor neutrophil response according to the current criterion, but such an improvement may not be meaningful or reproducible.

The proposed major neutrophil response criterion, “For absolute neutrophil count (ANC) less than 1500/mm³ before therapy, at least a 100% increase, or an absolute increase of more than 500/mm³, whichever is greater”, is cumbersome. We understand a need for a clearly defined absolute minimum increase in ANC but do not appreciate a need for the additional inclusion of a minimum percentage increase. A hypothetical patient with MDS who began a trial with an ANC of 1000/mm³ and whose ANC...
improved to 1900/mm\(^3\) would not qualify as a major response according to the proposed criteria, but the latter value for ANC is normal in many laboratories and such increments are associated with a decrease in the risk of infection.\(^6\)\(^7\) In addition, a hypothetical MDS patient starting a trial with an ANC of 800/mm\(^3\) whose ANC improved to 1500/mm\(^3\) would count as only a minor response according to the proposed criteria but would qualify as a major response if the count were 1600/mm\(^3\); the difference between these 2 responses is of questionable physiologic relevance. Although we recognize that all proposed response criteria must incorporate arbitrary numbers to a certain extent, deleting the percent response clause could minimize the degree of arbitrariness in the proposed major neutrophil response criterion.

Finally, we feel that the consensus neutrophil response criteria (both minor and major) should include a caveat that any responses observed should not be attributable to the use of corticosteroids. Some recent clinical trials in patients with MDS have included dexamethasone as a therapeutic agent and have classified patients as responding to the study regimen on the basis of an increment in the ANC alone. But neutrophil increments in patients taking corticosteroids are thought to represent leukocyte demargination and egress from the bone marrow of part of the storage pool of neutrophils, not a genuine increase in the synthesis of early leukocyte precursors.\(^8\) These increases do not correlate with improved clinical outcomes.

A simpler and more physiologically relevant neutrophil response criterion might include the requirement for an absolute increase in the ANC of 500/mm\(^3\) for any type of response and the requirement for normalization of the ANC (ANC of at least 1500/mm\(^3\)) for a major response.

**Clarifications of response criteria in myelodysplastic syndrome**

Steensma et al have raised several issues regarding the response criteria after therapeutic interventions proposed for myelodysplastic syndromes, which we are pleased to help clarify. Their first issue concerns the possible daily fluctuations that may occur in the neutrophil counts of patients with myelodysplastic syndrome (MDS). Although such fluctuations in the absolute neutrophil count (ANC) have been shown in patients without MDS but not in patients with MDS, our proposals indicate the need to document several observations of neutrophil counts before and after therapy to determine a response (minor or major). Because responses also require a duration of at least 2 months to qualify for that response category, the vagaries of such potential variations would thus be greatly diminished. An ANC rise from 100/mm\(^3\) to 200/mm\(^3\) (100%) is potentially clinically useful, given the association between degree of neutropenia with infection risk.\(^1\)

Their second point concerns the major neutrophil response criteria. Although necessarily arbitrary, a substantive biologic and clinical effect is believed to be warranted to be considered a major response. Our criteria were aimed to assure a clinically relevant rise for both very low ANCs (thus the net ANC increment criterion), but being more stringent for higher ANCs (eg, with baseline ANCs above 1000/mm\(^3\)), thus the percentage requirement. This criterion has also been used previously to determine neutrophil responses to granulocyte colony-stimulating factor.

Regarding their third point, we agree that the increments in ANCs should not be considered responses if attributable to steroids. If a corticosteroid is being used, this point should be clearly delineated in the study design. As we learn more about the clinical impact of specific therapies on MDS, we hope to be able to further refine these response criteria.

**Response:**

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**References**

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