were found to have an elevated transferrin saturation in her study of 10,500 blood donors from South Wales. This result differs from results in other studies in which an elevated transferrin saturation detected the predicted frequency of Cys282Tyr homozygotes in both a population of blood donors and in 65,000 individuals older than 20 years in a Norwegian county. The precise value of the transferrin saturation to be used as a “threshold” value in screening studies has been modified since our original study of blood donors. A value for the transferrin saturation of 50% for women and 55% for men is now widely accepted, recognizing that a small proportion of heterozygotes will be identified using these values.

Our previous report describing clinical penetrance of the Cys282Tyr homozygous genotype involved the study of 214 homozygous relatives of 291 homozygous probands. Our study differs from most published studies in that criteria for penetrance were restricted to a limited set of objective findings. Nearly every homozygote identified underwent liver biopsy, and fibrosis or cirrhosis was considered an indicator of penetrance. Many individuals with abnormal liver biopsies were completely asymptomatic. We also used radiographic evaluation of the metacarpal-phalangeal joints and found that hemochromatotic arthropathy was quite common and that the presence of arthropathy did not correlate well with total-body iron burden. We recognized the importance of familial factors influencing penetrance, and calculated our minimal estimate of the incidence of clinical penetrance to homozygous relatives of healthy probands who had been detected in screening studies. In this population, we estimated the incidence of clinical penetrance of 29% in men older than 40 years and 11% in women older than 50 years. We believe this estimate does reflect the incidence of penetrance in the white population.

Our results have been confirmed by Dr Sigvard Olsson and colleagues, who identified 297 potential homozygotes in central Sweden using an elevated transferrin saturation as the screening probe (written personal communication, June 2003). Liver biopsy was part of the evaluation, and fibrosis was found in 12.8% and cirrhosis in 5%. Thus, approximately 18% of the homozygotes identified had histologic evidence of iron-associated liver damage. These values approach the results we reported, indicating that our findings in the population of Utah are likely applicable to Cys282Tyr homozygotes elsewhere.

Defining the incidence of clinical penetrance of hemochromatosis is important in order to justify large-scale screening programs, but the key issue is that some fraction of homozygotes clearly suffer morbid complications. Until modifier genes are identified, it will be difficult to determine which homozygotes are destined to develop morbid complications and which are not. Thus, it remains important to identify homozygotes and initiate iron-depletion treatments before disease-related morbidity develops.

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References

To the editor:

Guidelines for the use of epoetin in cancer patients: a much-needed step forward in standardizing anemia treatment

Recently, clinical practice guidelines for the use of epoetin alfa in cancer patients were published. Although based on high-quality evidence, the rapid pace of research in anemia management requires that such guidelines be reviewed and updated regularly. This letter reviews new data, specifically on anemia-related quality of life (QOL) and optimal hemoglobin (Hgb) management, which are relevant to, and may serve to augment, the guidelines.

Recently, clinical practice guidelines for the use of epoetin alfa in cancer patients were published.1 Although based on high-quality evidence, the rapid pace of research in anemia management requires that such guidelines be reviewed and updated regularly. This letter reviews new data, specifically on anemia-related quality of life (QOL) and optimal hemoglobin (Hgb) management, which are relevant to, and may serve to augment, the guidelines.

Although the guidelines endorse epoetin alfa’s ability to improve hematologic outcomes, they do not support a relationship between epoetin alfa treatment and QOL improvements, primarily due to methodologic concerns regarding clinical studies; however, there is new evidence to consider. An a priori, planned, multivariate analysis of QOL data from Littlewood et al,2 accounting for possible confounding variables including disease progression, still indicated significant (P < .05) improvements in QOL for all 5 cancer-specific scales. A more conservative analysis by Fairclough et al,3 using joint-mixed effects modeling to account for nonrandom missing data, produced significant between-group differences in QOL scores comparable with those previously reported.

There were 2 studies published after the guidelines based on Littlewood et al’s data2 that examined the clinical significance of QOL improvements in patients receiving epoetin alfa. Patrick et al used change in Hgb level as an internal standard to determine the minimally important difference in QOL that could be considered clinically meaningful.5 Differences in QOL scores between the epoetin alfa and placebo groups exceeded these minimally important differences, supporting their clinical relevance. Cella et al compiled population-based reference QOL data from 10,788 persons in the United States via an internet survey.6 Comparison of the survey results with the Littlewood et al data2 showed that epoetin alfa treatment overcame 49% to 95% of the QOL deficit seen in anemic cancer patients compared with the population-norm sample. The Patrick et al and Cella et al analyses address the concerns of the guidelines and provide additional support for the beneficial effects of epoetin alfa on QOL in anemic cancer patients.

Selecting the optimal Hgb level for intervention is critical for maximizing patient benefits related to epoetin alfa treatment. The guidelines make a conservative recommendation (Hgb ≤ 100 g/L [10 g/dL]) based on published reports from clinical trials meeting strict criteria. However, the guidelines also state that epoetin alfa administration in patients with Hgb levels of 100 to 120 g/L (10-12 g/dL) should be determined by clinical circumstances. One retrospective analysis2 and 2 prospective trials published as abstracts6,7 provide strong evidence that early intervention with epoetin alfa prevents declines in Hgb level and QOL. A retrospective analysis of the Littlewood et al data2 prospectively stratified by...
Hgb level (Hgb > 105 g/L [10.5 g/dL] or ≤ 105 g/L [10.5 g/dL]) showed a similar mean increase in Hgb level from baseline for the higher and lower Hgb strata at 4 weeks and at last value; however, the transfusion rate was relatively lower in the higher Hgb stratum (7.1% compared with 28.2% for the ≤ 105 g/L [10.5 g/dL] stratum). The proportion of responders (patients with Hgb level increase ≥ 20 g/L [2 g/dL]) was also greater in the higher stratum (80.5% vs 68.5% in the ≤ 105 g/L [10.5 g/dL] stratum). With respect to cost effectiveness, fewer patients in the higher (15%) versus the lower (25%) stratum required doubling of their starting dosage.

Interim results of an open-label randomized trial in patients with hematologic malignancies and Hgb levels of 100 g/L (10 g/dL) or more and 120 g/L (12 g/dL) or less show a positive effect of epoetin alfa. Patients were randomized to either once-weekly epoetin alfa immediately (EPO) or to observation, during chemotherapy, with epoetin alfa offered if Hgb level decreased to less than 90 g/L (9 g/dL) (OBS). From baseline to end of treatment, the EPO group experienced significant increases in Hgb level (P = .007) and improvements in QOL. Furthermore, patients in the EPO group had a significantly greater decrease in clinic visits (P = .002) and days requiring assistance (P < .001), suggesting that treatment of mild anemia (Hgb 100-120 g/L [10-12 g/dL]) may reduce health care resource utilization.

Final results, not yet peer-reviewed, from a double-blind, placebo-controlled clinical trial in breast cancer patients receiving adjuvant or neoadjuvant chemotherapy, support efficacy of early intervention. Breast cancer patients with mean Hgb levels of 128 g/L (12.8 g/dL) receiving once-weekly epoetin alfa experienced an improvement in Hgb levels (+8 g/L [+0.8 g/dL]) after 16 weeks, and attenuated declines in both QOL and fatigue versus patients receiving placebo. In contrast, patients receiving placebo experienced a more than 20 g/L (2 g/dL) mean decrease in Hgb level after 2 cycles of anthracycline-based chemotherapy. Therefore, studies in patients with diverse malignancies suggest that epoetin alfa can maintain or improve Hgb level, and QOL, and decrease transfusions in patients with baseline Hgb level more than 100 g/L (10 g/dL). These results suggest a basis for a stronger recommendation regarding epoetin alfa use in patients with Hgb levels higher than 100 g/L (10 g/dL).

The focus of this letter is to draw attention to developments in 2 critical areas of anemia management: anemia-related QOL and optimal Hgb management. New analyses and data are relevant and may serve to augment the guidelines. As standards of care in anemia management continue to evolve, consideration of emerging data will be an essential part of the review process for clinical practice guidelines.

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References


To the editor:

Expression of Fcγ receptors type II (FcγRII) in chronic lymphocytic leukemia (B-CLL)

We have read with interest the paper from Damle et al analyzing the surface membrane phenotype of B lymphocytes in chronic lymphocytic leukemia (B-CLL). The authors stated that the leukemic cells from all B-CLL patients evaluated (irrespective of immunoglobulin heavy chain (IgVH) gene mutational status) bear the phenotype of antigen-experienced B cells based, among other features, on the very low expression of Fcγ receptors type IIb (FcγRIIb, CD32), which is the main isoform of FcγRII in B lymphocytes. We would like to comment on this issue on the basis of our own results, which differ from those of Damle et al.

We analyzed membrane expression of FcγRII by flow cytometry in leukemic cells from 52 B-CLL patients who were classified by Rai stage system as indolent (0-I), intermediate (II), or aggressive (III-IV) disease. We have used 3 different monoclonal antibodies (mAbs): clones AT10 and 2E1, which recognize all isoforms of FcγRII; and clone IV.3, which recognizes FcγRIIa when used as Fab fragment but is capable of reacting with FcγRIIb when used as a whole molecule. IV.3 Fab was tested because, to our knowledge, it is the only mAb capable of discriminating between FcγRII isoforms by fluorescence-activated cell sorter analysis; in fact, mAb IIb2 used by Damle et al has been shown to react with both isoforms. By using IV.3 Fab, we found that FcγRIIa is expressed only marginally in B-CLL cells from some patients (data not shown). On the other hand, more than 95% of leukemic cells, in all samples analyzed, were stained with mAbs AT10, 2E1, or IV.3 (whole molecule), which can be attributed to the