line and were thus excluded as not being clearly premenopausal. After the inclusion of women who had at least 1 year of follow-up and for whom menstrual-history data were sufficient at 12 months, the final study populations included 1885 women for overall survival and 1837 for disease-free survival. Among women with amenorrhea, there was significant improvement in overall survival (hazard ratio for death, 0.72; P=0.04) and in disease-free survival (hazard ratio for disease recurrence, a second malignant condition, or death, 0.65; P<0.001) (Fig. 1A and 1B).

We also performed a 12-month landmark analysis for subgroups of patients on the basis of their estrogen-receptor (ER) status. Women with ER-positive tumors who had amenorrhea had a significantly better outcome than those who did not have amenorrhea, with a hazard ratio for death of 0.52 (P=0.002) and a hazard ratio for disease recurrence, a second malignant condition, or death of 0.51 (P<0.001). By contrast, women with ER-negative tumors had a similar outcome regardless of whether they had amenorrhea, with a hazard ratio for death of 1.08 (P=0.76) and a hazard ratio for disease recurrence, a second malignant condition, or death of 0.96 (P=0.85).

In the landmark analysis, the percent differences in drug doses between women with amenorrhea and those without amenorrhea were small (Fig. 1C). When the differences were evaluated according to tumor ER status, study group, and specific drug, there was only one instance in which the relative difference was more than 3.8%. (In this instance, there was a relative increase of 9.7% in the dose of docetaxel received as part of sequential chemotherapy by women with ER-positive tumors who had amenorrhea.)

Thus, premenopausal women in whom amenorrhea developed as a consequence of adjuvant therapy had significantly better overall survival and disease-free survival than did women without amenorrhea, particularly when the tumor was ER-positive. Furthermore, the dose of the chemotherapy drug that was delivered was not a key factor in explaining the differences.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Paroxysmal Nocturnal Hemoglobinuria — Hemolysis before and after Eculizumab

TO THE EDITOR: The letter to the Editor by Berzuini et al. (Sept. 2 issue)[1] shows in a single example that in patients with paroxysmal nocturnal hemoglobinuria (PNH) who are receiving eculizumab, intravascular hemolysis is abrogated, but extravascular hemolysis becomes apparent, consequent to C3 binding to red cells, specifically to the red cells with the PNH phenotype, since they lack CD55. Two series involving 41 patients[2] and 31 patients[3] had already shown that this interesting phenomenon has been observed regularly in patients with PNH who are receiving eculizumab. Decreased red-cell survival measured in vivo[2] provided definitive proof of a hemolytic process.

However, from the letter to the Editor by Berzuini and colleagues, readers may get the impression that C3 binding on PNH red cells is automatically a major clinical problem and that prednisone is the answer. We are concerned about such an impression for three reasons. First, in most patients, this phenomenon has relatively little clinical relevance. For instance, an adequate level of hemoglobin may be maintained in a patient even when up to 80% of the PNH red cells have bound C3 (Fig. 1). Second, patients with PNH are facing a long course: in the past, many of them have had a variety of serious side effects of long-term use of glucocorticoids (such as "moon face" appearance, diabetes, hip necrosis, and even severe infection), despite the lack of evidence that the use of these agents was of any benefit.[4] Third, in the patient reported on by Berzuini et

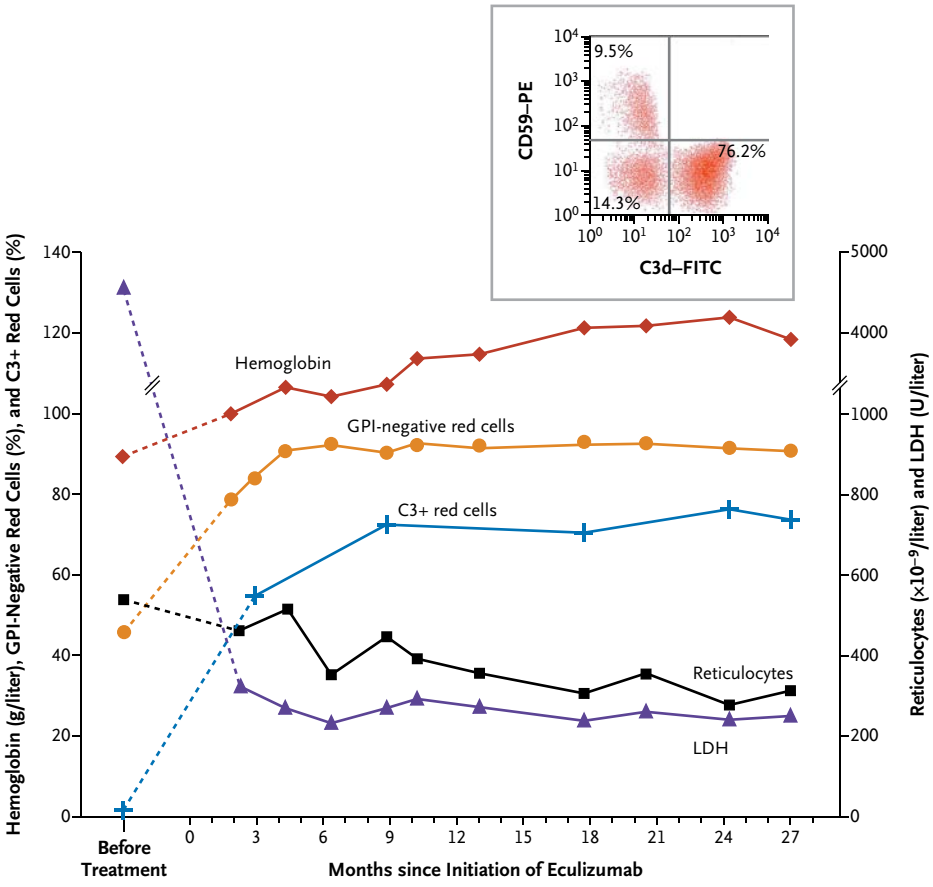

Figure 1. Clinical Course of a 50-Year-Old Patient with Severe Hemolytic Paroxysmal Nocturnal Hemoglobinuria.
From the time of diagnosis in 2004, the patient required an average of 3 units of packed red cells per month until May 2008, when she began to receive eculizumab treatment. After approximately 2 years, apart from normalization of the lactate dehydrogenase (LDH) level, there was an increase in glycosylphosphatidylinositol (GPI)–negative red cells; concomitantly, the steady-state hemoglobin level was approximately 12 g per deciliter, despite the fact that 76% of red cells (or 84% of PNH red cells) had bound C3d (see the inset, which shows the results of the flow cytometric analysis of the C3d deposition on a proportion of CD59 cells from the same patient). The reticulocyte count remained elevated, indicating continued extravascular hemolysis. The patient did not receive glucocorticoids. FITC denotes fluorescein isothiocyanate, and PE phycoerythrin.

al., the follow-up is far too short to prove that prednisone is beneficial. If prednisone is to be used to control extravascular hemolysis in patients with PNH who are receiving eculizumab, this should be done in the context of a clinical trial. Our experience with 14 patients suggests that this approach is not effective. In one patient, splenectomy was successful,[5] but this operation is not free of risk (in terms of thrombosis and otherwise), and it cannot be recommended as a routine approach.

Fortunately, even the minority of patients who, in terms of hemoglobin level, have only a limited response to eculizumab usually have improvement in symptoms such as abdominal pain and dysphagia, and the risk of thrombosis is probably decreased considerably among them, regardless of their extravascular hemolysis. Eventually, C3-mediated extravascular hemolysis might be overcome by a new intervention appropriately targeting C3. In the meantime, the last thing one would want is to have these patients burdened by the side effects associated with the long-term use of glucocorticoids (including a higher risk of infection), in addition to their infusions of eculizumab every 2 weeks.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following:

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CORRECTIONS

Case 27-2010: A 73-Year-Old Woman with Chronic Anemia (September 9, 2010;363:1060-8). In the first paragraph of the Treatment Goals subsection of Discussion of Management (page 1065), the fourth sentence should have read "Two — azacitidine and decitabine — are hypomethylating agents, which are thought to reactivate genes silenced due to hypermethylation in myeloid precursors," rather than ". . . agents, which inactivate genes associated with proliferation and survival in myeloid precursors." The article has been corrected at NEJM.org.

Performance of Common Genetic Variants in Breast-Cancer Risk Models (March 18, 2010;362:986-93). In Table 3 (page 990), the chromosome listed for the RS3803662 SNP should have been 16q, rather than 10q, and the chromosome listed for RS889312 should have been 5q, rather than 16q. The article has been corrected at NEJM.org.

Mortality Attributable to Smoking in China (January 8, 2009; 360:150-9). In the sixth paragraph of the Discussion section, beginning "Ezzati and Lopez estimated . . ." (page 156), the parenthetical information should have been given in thousands, rather than millions. The article has been corrected at NEJM.org.

NOTICES

Notices submitted for publication should contain a mailing address and telephone number of a contact person or department. We regret that we are unable to publish all notices received. Notices also appear on the Journal's *Web site (NEJM.org/medical-conference). The listings can be viewed in their entirety or filtered by specialty, location, or month.*

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