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# Epoetin Alfa: To Give or Not to Give

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In this issue of the Journal, Moebus et al. (1) reported that an erythropoiesis stimulation agent (ESA) can safely treat chemotherapy-induced anemia in breast cancer patients receiving adjuvant therapy. Earlier evidence of a potentially negative effect on outcomes has made this treatment controversial, and ESAs in general have not been indicated for use in the curative setting. The setting for their report was an Arbeitsgemeinschaft Gynokologische Onkologie (AGO) phase III randomized trial that tested dose intensity and density for 1284 patients with 4 or more positive nodes. Half were randomly assigned to treatment with intense dose-dense (IDD) epirubicin (E at 150 mg/m<sup>2</sup>) × 3 → paclitaxel (T at 225 mg/m<sup>2</sup>) × 3 → cyclophosphamide (C at 2500 mg/m<sup>2</sup>) × 3, all administered every 2 weeks with granulocyte colony stimulating factor and the other half to EC (90/600 mg/m<sup>2</sup>) × 4 → P (175 mg/m<sup>2</sup>) × 4 every 3 weeks (2). At a median follow-up of

5 years, the relapse-free survival (RFS; 70% vs 62%; *P* < .001) and overall survival (OS; 82% vs 77%; *P* = .03) were in favor of IDD chemotherapy. Not surprisingly, there were more nonhematologic and hematologic toxicities with the IDD regimen. With a longer follow-up of 10 years, these benefits were still maintained (3).

To test epoetin alfa (Epo), the authors performed a second randomization among the 643 patients in the IDD ETC arm to receive Epo or not. Epo was given three times a week to maintain a hemoglobin (Hgb) level of 12.5 to 13 g/dL, stopped when the Hgb was greater than 14 g/dL, and restarted when it was less than 13 g/dL. Patients with a Hgb of less than 9.0 g/dL were considered for transfusions on both arms of the study. The median duration of Epo administration was 18 weeks. The authors concluded that the use of Epo was beneficial because it prevented the otherwise typical 2.2-g/dL Hgb drop from cycle 1 to cycle 9 of chemotherapy and

was associated with a lower transfusion requirement (13% vs 28%). They also concluded that Epo was not associated with any negative impact on 5-year RFS (71% vs 72%;  $P = .86$ ) or OS (83% vs 81%;  $P = .89$ ) for control and Epo groups, respectively. In terms of toxicities, not surprisingly the venous thromboembolic rate was statistically significantly worse with the use of Epo (7% vs 3%;  $P = .03$ ). Based on their findings, the authors recommend that clinicians consider Epo use for the prevention of chemotherapy-induced anemia.

The question for clinicians is how convincing are their data? Of note, prior preclinical and clinical data on the effects of ESAs on tumor progression and overall outcomes were mixed (4). These findings could have been because of important limitations on the quality and assessment of the prior studies, but overall, several large studies suggested a worrisome trend toward increased rates of disease progression and death in patients on ESAs (4,5). Consistently across these trials there was an increased incidence of venous thromboembolic events associated with the use of ESAs. On the other hand, in early-stage breast cancer, two adjuvant treatment trials showed no excess mortality with ESAs. One was the ARA Plus trial, and the other was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-38 study (6,7). However, only ARA Plus was a randomized study. In contrast, worsened outcomes were noted in the Preoperative Epirubicin Paclitaxel Aranesp (PREPARE) trial conducted in the neoadjuvant setting. Here, dose-dense, dose-intense chemotherapy was tested in 733 patients with a second randomization that assigned patients to receive darbepoetin or not, with a goal of maintaining a Hgb concentration between 12.5 and 13 g/d (4,8). At a median follow-up of 3 years, outcomes appeared numerically (but not statistically) worse in the darbepoetin arm, with disease-free survival rates of 74% vs 80% ( $P = .06$ ) and OS rates of 88% vs 92% ( $P = .14$ ).

Where does this leave us? Is it safe and advisable to maintain Hgb using an ESA in the adjuvant setting? To answer these questions requires convincing data of safety. In that regard, there are several potential limitations to consider in the report by Moebus et al. (1). First, the subanalysis within the IDD chemotherapy arm was planned a priori to assess whether there was a difference in RFS and/or OS by ESA. Based on provided results of the trial, the null hypothesis (that there was no difference) could not be rejected given the study parameters. For OS the hazard ratio was 0.97 with a 95% confidence interval of 0.67 to 1.41, and for RFS the hazard ratio was 1.03 with a 95% confidence interval of 0.77 to 1.37. However, failure to reject the null hypothesis is not the same as saying that there is no difference. To prove that there is no difference in RFS and OS, one would need to test for equivalence, which would require a much larger sample size. Simply put, the sample size of 643 is not large enough to confirm equivalence in RFS or OS, and therefore, this subset analysis is most likely underpowered to rule out a negative effect from Epo. Second, this study demonstrated an unacceptably high rate of transfusion requirement of 28% with IDD ETC, and even with the use of Epo, the transfusion rate was only reduced to 13%. In their earlier report, Citron et al. reported the results of the Cancer and Leukemia Group B (CALGB) 9741 study, demonstrating that dose-dense chemotherapy given every second week was superior to the every third week schedule (9,10). Here, the transfusion rate was also 13% in the dose-dense arm, but this was seen without the need for ESA usage. Hence, a 13% requirement for

red blood cell transfusion despite the use of an ESA may reflect the use of higher doses of chemotherapy in the Moebus et al. (1) study. For example, the cyclophosphamide dose of 2500 mg/m<sup>2</sup> was likely contributing to the substantial anemia seen in this study, requiring Epo or transfusion support. Notably, earlier NSABP trials (NSABP B-22 and B-25) demonstrated that there was no improvement in outcomes when this chemotherapy agent was escalated from the standard dose of 600 mg/m<sup>2</sup> to 2400 mg/m<sup>2</sup> (11,12). Based on this earlier work, the high dose of cyclophosphamide used by Moebus et al. (1) may be unnecessary. If this is contributing to the relatively high rate of transfusion, despite the ESA usage, then this would be an important discussion point when interpreting the results of their study clinically. The third issue concerns cost. Can we justify adding ESAs as “prevention” when they do not improve RFS or OS or reduce the cost of care? The fourth and final concern is the more than doubling of the venous thromboembolic event rate (7% vs 3%) in this report. This may be unacceptably high given that earlier chemotherapy regimens have not demonstrated this level of risk (9).

Overall, this study provides important evidence that ESAs may be safe in the curative treatment of cancer. However, at the same time we must acknowledge that the data are insufficient to support the routine use of ESAs in this setting. The authors should be congratulated for addressing this important issue (with implications beyond breast cancer) as well as for providing additional evidence (in the parent trial) supporting the effectiveness of dose-dense scheduling.

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## An Organismic View of Cancer

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There is an association between glucose intolerance and pancreatic cancer (1), but the nature of the relationship remains unclear. In this issue of the Journal, Wolpin et al. (2) report the results of a nested case-control study. They found that in a multivariable model with mutual adjustment for HbA1c, insulin, and proinsulin, their biomarker for hyperglycemia, HbA1c, and their biomarker for impaired pancreatic beta-cell function, the plasma proinsulin/insulin ratio, were not associated with pancreatic cancer, whereas their biomarker for peripheral insulin resistance, plasma proinsulin, was related with pancreatic cancer. Wolpin et al. (2) go on to say that their biomarker for peripheral insulin resistance was elevated before the detection of the pancreatic cancer, which suggests that peripheral insulin resistance preceded the clinical detection of pancreatic cancer and was involved in its etiology. In other words, peripheral insulin resistance may predispose patients to pancreatic cancer, and correcting insulin resistance may prevent pancreatic cancer.

Causal factors, factors directly related to the etiology of the disease, should be accurate predictors of the disease they cause (3). Although Wolpin et al. (2) demonstrate a statistically significant relationship between pancreatic cancer and proinsulin, the fact that a relationship exists between the parameter/variance estimates of the independent variable and the dependent variable and that the relationship is unlikely to have occurred by chance does not entitle us to conclude that the independent variable is an accurate predictor of the dependent variable. In other words, statistical significance is not predictive accuracy. What was the discriminative accuracy of proinsulin? Wolpin et al.'s marker of peripheral insulin resistance added only 0.04 to the baseline model receiver operating characteristic of 0.59 (see Supplementary Table 3 for the article). This result was not statistically significant and is not clinically important. Furthermore, the baseline accuracy was only slightly better than flipping a coin at predicting pancreatic cancer. Therefore, in terms of predictive accuracy, it is unlikely that peripheral insulin resistance caused pancreatic cancer.

More interestingly, Wolpin et al. (2) claim that the physiology of the body is involved in the etiology of the disease. This contrasts with a tumor-centric model of cancer, which states that we should focus on the tumor. Regardless of whether peripheral insulin resistance is a cause of pancreatic cancer, an organism-centric perspective is important.

The tumor-centric model of sporadic solid cancers asserts that risk factors affect tissue by their action on cells' transcriptomes and once we know that effect we can reduce the risk of incident disease. Further, when the genomics of a tumor are known, we may be able control and defeat the cancer. Clearly, the immune system and other systems affect and are affected by the cancer—but they are usually viewed from the perspective of the cancer. This perspective is similar to a geocentric model of the solar system, where the sun revolves around the earth, or in this case, the tumor.

Another cancer model can be called “organismic.” In this view, the body is a unitary system. The solid tumor arises within and is a functional component of the body. In the organismic model, the body is the proper unit of analysis. This is similar to a heliocentric model where a planet is part of a larger, integrated system and its motion cannot be properly understood apart from the larger system.

The body can be viewed as an organism that is composed of integrated, mutually interdependent, functional components, all of which must operate properly if the body is to maintain physiologic homeostasis. The body gives rise to the tumor, and the body uses its regulatory systems to maintain homeostasis in the face of the disequilibria caused by the tumor. In other words, the tumor is not an isolated entity; it is an integral part of a larger system. The organismic view is interactional. The maturing tumor perturbs the system, and the system attempts to adapt to it, which includes ameliorating its effects, and the body tries to control it, which involves trying to stop it from gaining biological and physiological dominance. The body and tumor interact with