

Re: Acute Myeloid Leukemia or Myelodysplastic Syndrome Following Use of Granulocyte Colony-Stimulating Factors During Breast Cancer Adjuvant Chemotherapy

The recent article in the Journal by Hershman et al. (1) reports on rates of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) among women with breast cancer following treatment with chemotherapy and granulocyte colony-stimulating factors. This analysis, based on Surveillance, Epidemiology, and End Results (SEER)–Medicare data, uses women treated with chemotherapy alone as the comparison group. Both the article and the accompanying Editorial (2) state that Medicare claims have not been validated and that it is not known how sensitive the claims information in the SEER Program database is for primary cancers. These statements could lead to a misunderstanding of the data and require clarification.

The SEER data include information reported from population-based registries. The registries abstract information from the medical record of persons who are newly diagnosed with cancer. SEER data undergo extensive quality assessment and have been found to have complete and reliable case ascertainment and staging (3). The SEER data include no health care claims and use International Classification of Diseases for Oncology codes to identify newly diagnosed cases.

To augment information collected by the registries, the National Cancer Institute has linked persons in the SEER data to Medicare enrollment files; 93% of persons aged 65 years and older in SEER have been linked to Medicare data. Procedure codes found on Medicare claims, including chemotherapy, have been shown to have good agreement with the medical record (4–7). Diagnostic codes on Medicare claims have been shown to have high positive predictive value for specific conditions, although the sensitivity of the data varies from low to high.

In their analysis, Hershman et al. (1) used diagnoses from the Medicare data to

identify the occurrence of MDS and AML. To address concerns about the validity of the reporting of these conditions in the Medicare claims, the authors performed a sensitivity analysis, evaluating how requiring two or more claims of MDS or AML would affect their findings. They report that there was no change in the hazard ratio, although they do not report the specific point estimates, which would have allowed readers to judge the differences themselves. Findings from the earlier validations of Medicare data suggest that claims with MDS and AML codes have a high positive predictive value, with unknown sensitivity. If the sensitivity were low, the estimates reported in the study by Hershman et al. would be a lower bound.

Large population-based observational datasets, such as SEER–Medicare data, are not intended to provide definitive information about treatment outcomes. Rather, these data can be used to target more in-depth clinical evaluations. To use Medicare or SEER–Medicare data correctly and interpret the findings from analyses using these data, it is important that researchers and readers have to have an accurate understanding of the quality of the files.

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Hershman et al. (1) reported an increased risk (hazard ratio [HR] = 2.14) of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) among women with breast cancer aged 65 years or older included in the Surveillance, Epidemiology, and End Results (SEER)–Medicare database who were treated with adjuvant chemotherapy and received granulocyte colony-stimulating factors (G-CSFs) or granulocyte–macrophage colony-stimulating factors as compared with those who did not. Two randomized studies (2,3), evaluating the efficacy of adjuvant G-CSF–supported dose-dense chemotherapy represent an ideal prospective model to verify the leukemogenic effect of G-CSF. Indeed, all patients in the experimental arms received G-CSF, whereas no patient in the control arms received it. In these studies, no increase in the risk of AML or MDS was observed.

Chance is an unlikely explanation for the observed difference between the study of Hershman et al., in which 16 cases of AML or MDS were diagnosed among 906 breast cancer patients treated with G-CSF,

for a cumulative incidence of 1.8% (95% confidence interval [CI] = 0.8 to 2.8) at 4 years and of 2.6% (95% CI = 1.3 to 3.9) at 7 years, and the two randomized trials, in which a total of five cases of AML or MDS were diagnosed in 1592 G-CSF-treated patients (0.3%, 95% CI = 0.1 to 0.7): five of 988 patients in the first study (0.5%, 95% CI = 0.2 to 1.1), at a median follow-up of 3 years, and 0 of 604 patients in the second study (0%, 95% CI = 0 to 0.6), at a median follow-up of more than 10 years.

A possible reason for the discrepancies between the results of the randomized studies and the data reported by Hershman et al. may be the different age of the patient populations and the consequently different baseline risks of AML and MDS. Because the SEER–Medicare database included only women aged 65 years and older, Hershman et al. analyzed only this elderly patient population, whereas the two randomized studies included patients of all ages. In the first study, women aged 60 years or older made up 17.5% of the population and women aged 70 years or older made up 2.5%; in the second study, women aged 65 years or older constituted 8.3% of the population.

Finally, the SEER–Medicare database did not record the dose and dose intensity of chemotherapy and therefore the analyses of Hershman et al. did not include the dose of alkylating agents used by the women. Retrospective evaluation of data from several other randomized trials (4) has shown an increased risk of AML or MDS with increasing dose of cyclophosphamide, as compared with the standard dose (the increase ranged from 2.45 to 6.81 as the dose increased, log-rank P value = .0002). A positive, non-statistically significant association was also seen between total dose of G-CSF and incidence of AML or MDS (HR = 2.34, 95% CI = 0.72 to 7.55). Given these findings, chemotherapy dose must not be excluded in the evaluation of the risk factors for AML or MDS because higher doses of chemotherapy are often associated with the use of G-CSF. In multivariable analyses, such as those performed by Hershman et al., residual confounding may arise when no adjustment for dose is performed. Thus, the association between AML or MDS and G-CSF may not be causal but could reflect the underlying use of higher dose of chemotherapy. The con-

tribution of G-CSF to the risk of AML or MDS following chemotherapy requires further study, but its use to support dose-dense chemotherapy that has been shown to improve breast cancer outcome remains appropriate.

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Response

We are grateful to the authors of the letters for the opportunity to clarify two issues that were addressed in the Discussion of our paper (1). The first issue, raised by Warren and Brown, addresses the quality and validity of the Surveillance, Epidemiology, and End Results (SEER)–Medicare database.

We agree with the authors that our statement implying that Medicare claims had not been validated was misleading. Our intent was to state that each case had not been validated in this particular study, and we thank the authors for clarifying the literature that justifies the methodology we used for the sensitivity analysis. They also clarify the utility of the SEER–Medicare database.

Clavarezza et al. address the issue of confounding by indication. As we mentioned in our Discussion, a major limitation of our study is that we could not measure dose and dose intensity for individual patients. However, as we stated, “Adjusting for type of chemotherapy, duration of chemotherapy, radiation exposure, and stage of disease had a minimal effect on the overall hazard ratio.” We also addressed the results of the Cancer and Leukemia Group B (CALGB) 9741 trial mentioned by Clavarezza et al., in which only 11 patients (0.5%) developed acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) after 3 years of follow-up (2). The risk of MDS/AML was the same in patients treated with dose-dense (every 2 weeks) chemotherapy with granulocyte colony-stimulating factor (G-CSF) as in patients treated with chemotherapy at 3-week intervals. Similarly, in the report by Venturini et al. (3), comparing 5-fluorouracil, epirubicin, and cyclophosphamide every 14 days with G-CSF with 5-fluorouracil, epirubicin, and cyclophosphamide every 21 days (control), patients in the control arm who developed bone marrow toxicity had their doses reduced or delayed and did not receive growth factors. Therefore, patients did not receive secondary prophylaxis with G-CSF in either of these trials. None of the patients in either arm of the trial of Venturini et al., consisting of more than 1200 patients followed for a median of 10 years, developed MDS/AML. These very low rates of MDS/AML are substantially lower than have been previously reported in similar clinical trials or in the general population, and the reduction may be related to the lower total dose of anthracycline and/or alkylating agents used in these studies or other selection criteria such as age. Interestingly, the study of Venturini et al., unlike that of the CALGB, did not find a survival benefit of dose-dense therapy administration.

Like all studies of the association between G-CSF and leukemia, our study was limited by our inability to control for confounding by indication. The purpose of G-CSF is to support the marrow in patients treated with more intensive chemotherapy regimens. The more dose intensive the adjuvant therapy regimen, the higher the risk of secondary leukemia.

There is no evidence that prophylactic use of growth factors increases the risk of AML/MDS, because the risk of this complication has not increased over time. We find this reassuring and believe that it supports the use of dose-dense therapy when indicated. The interactive effects of host factors, chemotherapy, and growth factors warrant further investigation, because a recent study now suggests that GM-CSF use may exacerbate the increased AML/MDS risk associated with certain types of chemotherapy in some patients (4). Further research is warranted to clarify the factors that increase the risk of this deadly complication of cancer treatment.

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