To the editor:

Incidence of second cancers after allogeneic hematopoietic stem cell transplantation using reduced-dose radiation

We read with interest the article by Rizzo et al[1] updating their earlier publication[2] and describing the largest international retrospective analysis of second cancers after allogeneic hematopoietic stem cell transplantation (HSCT) to date. Their data demonstrate a cumulative incidence of second malignancies of 3.3% at 20 years. The greatest risk of solid tumors, such as melanoma, breast, thyroid, brain, and other tumors, was age younger than 30 at the time of HSCT and total body irradiation (TBI). This higher risk associated with younger age at time of transplantation is similar to the results from atomic bomb survivors,[3] and these confirmatory data provide critical information in the counseling of patients considering HSCT. Their current analyses unfortunately grouped those who received doses below 12 Gy, and suggested that TBI doses lower than 12 Gy confer the same second cancer risk as TBI doses above 12 Gy. In contrast, previous analyses in atomic bomb survivors have shown a near-linear relationship between the TBI dose and second cancer risk, especially below 5 Gy.[3,4] Further, Curtis et al previously found that lower doses of TBI (< 12 Gy) were associated with a lower risk of second cancer.[2] Because a growing number of allogeneic HSCTs employ substantially lower doses of TBI, including doses as low as 2 Gy, this point deserves further clarification. An analysis focusing on the second cancer risk with lower doses of TBI would complement the atomic bomb survivor data and greatly benefit the transplantation community. Additionally, including the incidence of second cancers in patients with nonmalignant disorders, such as hemoglobinopathies or aplastic anemia, would further broaden the applicability of their extensive data analyses.

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Acknowledgments: This work was supported by the intramural research program of the National Heart, Lung, and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health (Bethesda, MD).

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Response:

Solid cancers after allogeneic hematopoietic cell transplantation

We appreciate the comments from Dr Hsieh et al, who raise an important issue regarding our recent publication.[1] They point out the apparent lack of a dose-response relationship between total body radiation dose and second cancer risk, where fractionated doses of less than 12 Gy or a single dose of 10 Gy were equally associated with elevated risks of solid tumors. This finding contrasts with data from the atomic bomb survivors in whom a near-linear dose response was demonstrated, albeit for a much lower range. Although Hsieh et al point out that the HCT community is increasingly using lower doses of radiation in the preparative regimen (reduced intensity and nonmyeloablative regimens), several important differences between our population and the atomic bomb survivors must be kept in mind. Approximately 99% of exposed members of the Life Span Study cohort of atomic bomb survivors received radiation doses less than 2 Gy,[2] which is considerably lower than the doses administered to transplant recipients in our study receiving myeloablative conditioning regimens. Other differences include the immunocompromised status of HCT patients, and differences in type and quality of radiation received.

Our study included patients whose procedures were performed before 1996. During that period of time, most patients received myeloablative preparative regimens with very few receiving TBI doses less than 5 Gy. In the single dose TBI group, there were actually no second cancers observed among the only 205 patients whose TBI dose was less than 5 Gy. Among the 1729 patients who received single doses of radiation between 5 and 9.9 Gy, there were 10 second malignancies. However, among the 111 patients who received fractionated TBI at doses less than 8 Gy, 2 second malignancies occurred, among the 522 who received between 8 Gy and 9.9 Gy, 3 cases occurred, and among the 2077 who received between 10 and 11.9 Gy, 12 cases occurred. As indicated, very small numbers of patients and extremely small numbers of "expected" events in the lowest radiation groups (< 5 Gy single or < 8 Gy fractionated total dose) make meaningful analyses difficult. This is unfortunate, as one theoretical advantage of the low doses of TBI in current reduced-intensity preparative regimens is a lower risk of therapy-related cancers. We agree with Hsieh and colleagues that a study that could determine whether this is, in fact, the case would be important. Meaningful analyses of these lower dose TBI regimens should be possible once a larger number of patients transplanted since the late 1990s has been followed for 5 years or longer. We intend to address the issue at that time.

The incidence of second cancers presented in this article included patients who received HCT for nonmalignant disorders, such as severe aplastic anemia (SAA; 10% of patients) and hemoglobinopathies (3%). Our Poisson regression analyses were stratified by age, disease, and time since HCT, because risks differ