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THE AUTHORS REPLY: We agree with Little et al. that clinicians should be aware of the risk of cardiovascular morbidity and limit the dose to the heart when performing radiotherapy for breast cancer. As pointed out by Liu et al., many radiotherapy centers already do this by means of techniques such as breath hold, by treating patients in the prone position (as indicated by Formenti et al.), or by intraoperative radiotherapy (as indicated by Vaidya et al.). We agree with Liu et al. that a comparison of benefits and risks is important in radiotherapy for breast cancer. As discussed in our article, the results of our study provide reassurance for the majority of patients that their absolute risk of heart disease from radiotherapy is likely to be small, as compared with the probable absolute benefit from radiotherapy.¹ Our results can also be used to identify the minority of patients for whom the benefits of radiotherapy do not clearly outweigh the risks.

In the cohort study² preceding our case-control study, we compared patients who underwent radiotherapy for the treatment of cancer of the left breast with those treated for cancer of the right breast, and we found an increased risk of aortic valvular disease among those with cancer of the left breast, with an incidence-rate ratio of 1.70 (95% CI, 1.14 to 2.53; $P=0.009$). Valvular disease was not a case-defining event in our case-control study, but in response to Toutouzias et al., we note that the study of valvular disease will require further work.

Formenti et al. comment on the method we used to estimate individual patient doses. Almost all the women who were included in our study were treated before the era of radiotherapy planning with the use of patient-specific scans based on CT, so our dose estimates could not take into account differences in anatomy. If we had been able to do so, it is likely that our estimated risks per gray would have been somewhat larger, but we do not know by how much. In order to identify the best possible treatment for each patient, clinicians need information on the absolute size of the benefits and on the absolute size of the risks. Our research group is continuing to develop methods to estimate the consequences of the cardiac doses delivered by old radiotherapy regimens, so that the experience of patients treated in the past can be used to provide clinicians with information on the absolute magnitude of the risks of current cancer treatments.

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Omalizumab for Chronic Urticaria

TO THE EDITOR: Maurer et al. (March 7 issue)¹ report the results of a phase 3 trial of omalizumab for the treatment of urticaria. Figure 1 of their article shows that withdrawals from the study because of "disease progression" occurred only in patients who received omalizumab; there were no withdrawals due to disease progression

in the placebo group. Furthermore, the percentage of patients who withdrew due to disease progression correlated with the dose of omalizumab (1% in the 75-mg group, 4% in the 150-mg group, and 8% in the 300-mg group); this suggests that omalizumab may itself, paradoxically, contribute to urticaria.

A review of the safety of omalizumab in patients with asthma, rhinitis, and other related diseases showed that urticaria occurred at the same frequency in the control group and the omalizumab group (1.3%).² However, in a long-term safety study involving children with asthma, 4.9% of patients in the omalizumab group were reported to have urticaria, and one patient had to discontinue omalizumab because of the severity of urticaria.³

The possibility that omalizumab causes or worsens urticaria needs to be considered.

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TO THE EDITOR: Maurer et al. reported as an exclusion criterion “a clearly defined underlying cause for chronic urticaria.” They did not mention the possibility that some patients could have high levels of circulating IgG directed against IgE or the IgE receptor. This condition can be revealed by an autologous serum skin test¹ in which a wheal appears about 15 minutes after an intradermal injection of the patient’s serum. A positive autologous serum skin test is present in almost one third of patients with chronic urticaria,² and treatments such as cyclosporine and glucocorticoids are known to be effective in these patients.³

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Maurer and colleagues provide data on the use of omalizumab in the treatment of chronic urticaria that is unresponsive to approved doses of antihistamines. Neither this study nor previous randomized studies^{1,2} compared omalizumab with high-dose antihistamines or immunosuppressive or immunomodulatory medications. Patients who receive such medications and have refractory disease are most in need of alternative therapeutic options.^{3,4}

We present a series of 30 patients treated with omalizumab for chronic idiopathic urticaria, chronic autoimmune urticaria, or other (physical) urticaria (Table 1). All patients had moderate-to-severe symptoms at least four times per week despite the use of immunosuppressive medications. After treatment with omalizumab, 10 patients had complete resolution of their symptoms, 8 had a significant response, 4 had a partial response, and 8 had no response. These findings provide evidence about the use of omalizumab in cases other than chronic idiopathic urticaria and in cases that are refractory to standard medications.

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Table 1. Characteristics of the Patients, According to Response.*

Variable	Complete Response (N=10)	Significant Response (N=8)	Partial Response (N=4)	No Response (N=8)
Age (yr)				
Mean	42	55	51	45
Range	23–54	39–73	31–81	20–70
Sex (no. of patients)				
Female	8	5	3	5
Male	2	3	1	3
Symptom duration (wk)				
Mean	69	158	156	200
Range	9–247	17–484	29–426	26–438
Urticaria diagnosis (no. of patients/ total no.)				
Chronic autoimmune†	4/10	5/8	1/4	2/8
Chronic idiopathic	5/10	2/8	3/4	4/8
Other‡	1/10	1/8		2/8
Coexisting condition (no./total no.)				
Atopy§	5/10	1/8	2/4	0/8
Asthma	5/10	1/8	1/4	0/8
Previous medications (no./total no.)				
High-dose antihistamine	10/10	8/8	4/4	8/8
Cyclosporine	7/10	6/8	2/4	7/8
Prednisone	7/10	7/8	2/4	2/8
Methotrexate	2/10	3/8	1/4	5/8
Sulfasalazine	2/10	4/8	0	3/8
Hydroxychloroquine	1/10	2/8	0	2/8
Dapsone	0	1/8	0	0
Intravenous immune globulin	1/10	0	0	0
Omalizumab dosage (no. of patients/ total no.)				
300 mg every 4 wk	9/10	7/8	4/4	8/8
225 mg every 2 wk	1/10	1/8	0	0
150 mg every 4 wk	0	0	0	0
Adverse side effects (no. of patients)	2¶	0	0	0

* A complete response was defined as resolution of symptoms and the ability to discontinue all previous medications. A significant response was the resolution of symptoms and the ability to discontinue all previous medications except antihistamines. A partial response was a decrease in symptom frequency and severity as well as the ability to decrease the dose of immunosuppressive agents. No response was no change in symptoms and an inability to taper or discontinue other medications.

† Chronic autoimmune urticaria was defined as the presence of a positive autologous serum skin test or chronic urticaria index.

‡ Other types of urticaria were solar urticaria (in the complete-response group), cold-induced urticaria (in the significant-response group), and cholinergic urticaria (in the no-response group).

§ Atopy was defined as the presence of a positive allergen-specific skin test or serum IgE.

¶ The side effects were lip swelling in one patient and an upper respiratory infection in another patient.

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THE AUTHORS REPLY: The suggestion by Wu and Long that there was a correlation between withdrawal rates and the dose of omalizumab is not supported by the study findings. First, the study withdrawals include withdrawals that occurred in the 12-week treatment period and the 16-week follow-up period (when no study treatment was administered). Indeed, all six patients in the group receiving 300 mg of omalizumab who withdrew because of disease progression did so during the follow-up period, and most withdrawals occurred more than 2 months after the last dose of omalizumab was administered. Second, the small numbers of patients who withdrew owing to disease progression (none in the placebo group, one in the 75-mg group, three in the 150-mg group, and six in the 300-mg group) preclude any conclusions about a dose-dependent relationship. Third, during the treatment period there were no study-drug-related or dose-related patterns in study-drug discontinuations because of disease progression (one in the placebo group [1.3%], three in the 75-mg group [3.7%], one in the 150-mg group [1.2%], and none in the 300-mg group).

We disagree that the findings of the pediatric study highlighted by Wu and Long suggest that omalizumab may contribute to urticaria. The urticaria rate was reported for the overall study (i.e., the 24-week double-blind period and the 28-week open-label extension), and hence there is no control value for comparison. In addition, extensive evidence indicates that omalizumab does not cause or worsen urticaria. As Wu and Long mention, another study involving more than 7500 patients with allergic disease showed that urticaria occurs infrequently in patients who receive omalizumab; the rate of urticaria among these patients is similar to the rate in the control group (both 1.3%). Furthermore, pooled data from two randomized, double-blind trials (of 28

and 52 weeks' duration) involving a total of 926 children with asthma showed that the incidence of urticaria was similar among patients who received omalizumab and those who received placebo (3.5% vs. 3.6%).¹

In response to Benelli and Ventura: anti-IgE-receptor antibodies were present in 29.3% of the patients in our study. Although it was not specifically evaluated here, previous studies have indicated that omalizumab is efficacious in patients with chronic autoimmune urticaria.^{2,3} Hence, omalizumab may provide a viable alternative to immunosuppressive medications and glucocorticoids, which are unsuitable for long-term use because of considerable side effects.

The study by Altman and Naimi indicates that omalizumab is effective in patients with chronic urticaria that is unresponsive to high-dose antihistamines plus additional medications. A phase 3 clinical trial of omalizumab (ClinicalTrials.gov number, NCT01264939) has been conducted in a similar patient population. The data presented by Altman and Naimi are consistent with case reports and small studies showing that omalizumab may be effective in refractory physical urticarias.⁴

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