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LETTERS TO THE EDITOR

IN REGARD TO ALLEN *ET AL.*: FATAL PNEUMONITIS ASSOCIATED WITH INTENSITY-MODULATED RADIATION THERAPY FOR MESOTHELIOMA (*INT J RADIAT ONCOL BIOL PHYS* 2006;65:640–645)

To the Editor: We read with interest the communication by Allen *et al.* (1) regarding trimodality mesothelioma treatment including intensity-modulated radiation therapy (IMRT) leading to six cases of fatal pneumonitis. The authors should be commended for publishing this report because it gives the radiation oncology community an opportunity to further reflect on the challenges of IMRT implementation in thoracic malignancies.

Two recent publications (1, 2) have reported Grade 5 radiation pneumonitis toxicity in association with novel approaches in the treatment of thoracic malignancies. We have identified 10 additional reported cases (3–6) of fatal pneumonitis in the non-small-cell lung cancer (NSCLC) dose–volume histogram (DVH)-radiation pneumonitis correlation literature. These events were associated with elevated V_{20Gy} or V_{25Gy} parameters in six cases that reported DVH characteristics. The authors of the current report correctly point out that it is difficult to draw dosimetric conclusions from their small patient numbers and lack of V_{5Gy} heterogeneity. It is interesting to note that 4 patients (Patients 1, 2, 6, and 7) had "high-risk" $V_{5Gy} \geq 90\%$ parameters that did not lead to clinically significant pneumonitis, and 1 patient (Patient 3) with relatively low V_{5Gy}, V_{20Gy}, and mean lung dose had a Grade 5 event.

Our understanding of the underlying genetic and cellular mechanisms mediating the expression of radiation pneumonitis is incomplete (7). In addition, we do not have robust clinical or dosimetric models to accurately predict, avoid, or mitigate clinically significant radiation pneumonitis. We operate with limited information about the influence of chemotherapy timing/delivery/agents, IMRT technique, and pre- and postpneumonectomy RT on both the ideal DVH parameters and radiation pneumonitis risk.

Dosimetric investigations have previously demonstrated increased V_{5Gy} parameters in conjunction with inverse planned IMRT (8, 9) for NSCLC. Our two institutions are prospectively evaluating the implementation of helical tomotherapy (HT) in the treatment of NSCLC. We have observed increased V_{5Gy} in routinely planned HT when compared with matched three-dimensional conformal radiotherapy back-up comparison plans ($n = 11$, HT $V_{5Gy} = 65\%$ vs. three-dimensional conformal radiotherapy $V_{5Gy} = 51\%$, paired t test $p = 0.03$). We continue to prospectively assess comparative dosimetry on each clinical case to select appropriate cases for image-guided HT.

Future investigations of thoracic IMRT in conjunction with dose/dose-per-fraction escalation, radiosensitizing chemotherapy in patients with limited pulmonary function (emphysema or pre- and postpneumonectomy), or large treatment volumes (mesothelioma, multifocal disease, or extensive primary/nodal coverage) should ideally be performed in the setting of prospective clinical trial or with rigorous institutional controls of confounding factors so as to properly assess acute/late toxicity and to make safety recommendations.

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IN REGARD TO ISHIKAWA *ET AL.*: CYCLOOXYGENASE-2 IMPAIRS TREATMENT EFFECT OF RADIOTHERAPY FOR CERVICAL CANCER BY INHIBITION OF RADIATION-INDUCED APOPTOSIS (*INT J RADIAT ONCOL BIOL PHYS* 2006;66:1347–1355)

To the Editor: The data presented by Ishikawa *et al.* (1) are appreciated because they confirm the effect of COX-2 expression on induction of apoptosis in response to radiotherapy (RT). However, some issues require discussion. The authors state that COX-2 inhibitors could represent a new approach for treating cervix cancer and they mention studies in which selective COX-2 inhibitors combined with RT have shown encouraging results without an increase in the risk of radiation-related toxicity (2, 3). However, they did not mention that two phase I/II studies have recently been published in cervix cancer combining the COX-2 inhibitor celecoxib with chemo-radiotherapy (CRT).

The Phase I Radiation Therapy Oncology Group 0128 study accrued 81 patients with advanced-stage cervix cancer, treated with celecoxib 400 mg twice daily for 1 year in combination with RT, cisplatin, and 5-fluorouracil (5-FU). Thirty-five of 75 patients (47%) experienced Grade 3–4 acute toxicity, which was mainly hematologic and gastrointestinal. This high rate, perhaps because of the addition of 5-FU to cisplatin, exceeded a toxicity threshold of 35% that was established in advance by the investigators and the regimen was therefore considered unacceptable for further clinical development (4).

In our institution, 31 patients were accrued to a phase I/II trial of celecoxib 400 mg twice daily 2 weeks before, and during RT- and cisplatin-based chemotherapy. Acute toxicity was not found to be significantly elevated but late toxicity (LT) was a concern: 3 of 31 patients (9.7%) developed Grade 4 recto-vaginal fistulas and 1 patient had Grade 3 vaginal necrosis (3.2%). The actuarial likelihood of Grade 3–4 LT at 2 years was 13.7% (5). In a recent retrospective article from our group, the 3-year probability of Grade 3–4 LT was only 7.6% and 6.9% for patients treated with RT alone and CRT, respectively (6). Therefore, in terms of our practice, these LTs are concerning. Furthermore, recognizing the limitations of a phase I/II trial, we were unable to demonstrate efficacy of celecoxib in addition to CRT by monitoring tumor biomarkers of response.

We believe that, although there is biologic rationale for combining

COX-2 inhibitors with CRT to treat patients with cervix cancer, our results and those from the Radiation Therapy Oncology Group trial suggest that the potential toxicity of COX-2 inhibitors on normal tissue probably offsets any small benefit that might exist. This is likely to constrain further investigation of these agents, and alternate biologic strategies for improving the outcome of these patients should be explored in combination with evolving techniques for more precise RT delivery.

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IN REPLY TO DR. HERRERA *ET AL.*

To the Editor: We appreciate helpful comments provided by Dr. Herrera and colleagues on our article. We would like to discuss the results of two recent phase I/II studies (1, 2) of cervical cancer treated with chemoradiotherapy (CRT) and celecoxib and respond to their questions.

First, regarding late toxicities, Herrera *et al.* reported a higher rate of Grade 3–4 late toxicities (13.4%) in the recent trial using celecoxib (1) compared with their historical data of CRT (6.9%) for cervical cancer (3). However, the data need to be carefully analyzed whether the increase in the rectal toxicities is solely due to the addition of celecoxib (400 mg twice daily for 8 weeks) to CRT: the irradiation dose at the rectum is recognized as the most significant risk factor for developing late rectal toxicity in radiotherapy (RT) for cervical cancer. Although RT schedule was similar in the two studies, brachytherapy by Herrera *et al.* was applied only with tandem applicator without the use of ovoid applicators; the relationship between the rectal dose and the rectal toxicities needs to be sufficiently analyzed in this case. Furthermore, the Radiation Therapy Oncology Group 0128 study (2) using the administration of high-dose celecoxib (400 mg twice daily for 12 months) demonstrated an increase in acute toxicity but not in the late rectal toxicity in comparison with the Radiation Therapy Oncology Group 9001 study. Therefore, Gaffney *et al.* indicated that further testing of celecoxib combined with CRT for cervical cancer is reasonable if promising efficacy is found without substantial increase in the late toxicities (2).

Second, there are some limitations in the studies of Herrera and Gaffney (1, 2) with regard to the efficacy of celecoxib (COX) in treating cervical cancer. In our study using pretreatment biopsy specimens, the COX-2 expression rate ranged widely from 1.0% to 87.9%. Although the expression of COX-2 was not examined in the Herrera and Gaffney studies, the essential benefit of COX-2 inhibitors on tumor response would be expected, especially for COX-2 expressing tumors. Similarly, gefitinib is significantly effective for lung cancer patients who have tumors with gene mutation in epidermal growth factor receptor (4).

In conclusion, if the appropriate dose and timing of celecoxib administration is elucidated, the use of celecoxib with RT may benefit cervical cancer patients with COX-2 expressing tumors. Even with the advantage of celecoxib, the optimal RT including brachytherapy should always be applied so that the irradiation dose to the rectum is limited to the minimum to avoid late rectal toxicities.

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IN REGARD TO MILLER *ET AL.*: MULTIPLE SCLEROSIS, BRAIN RADIOTHERAPY AND RISK OF NEUROTOXICITY: THE MAYO CLINIC EXPERIENCE (*INT J RADIAT ONCOL BIOL PHYS* 2006;66:1178–1186)

To the Editor: We read with interest the study of Miller *et al.* on the risk of neurotoxicity in multiple sclerosis (MS) patients receiving external beam radiotherapy (1). We have recently shown that approximately 45% of MS patients show reduced or absent constitutive expression of the ATM protein in the peripheral blood mononuclear cells. This subset of ATM-low MS patients showed defective activation of downstream proteins and, in particular, p53 (2). A case study of an MS patient with decreased levels of the ATM has been recently described. In that study, the MS patient and his unaffected father showed decreased constitutive levels of ATM in peripheral blood mononuclear cells and skin and increased sensitivity to radiation (3). We propose that in this subset of ATM-low MS patients, defective activation of the DNA damage pathway, is most likely responsible for the increased sensitivity to radiation.

We would suggest that MS patients and their immediate family members be evaluated for the expression of ATM when radiation therapy is being contemplated. We propose that this can be done easily in peripheral blood lymphocytes by flow cytometry. Individuals with low level of ATM would be at higher risk for radiation-induced neurotoxicity, and hence the radiation dosage should be reduced accordingly to decrease the incidence of radiation injury.

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