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Cetuximab and Radiotherapy for Head and Neck Cancer

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The treatment of head and neck cancer is complex and difficult, both technically and physically. Tumors in each site in the head and neck (oropharynx, hypopharynx, larynx, and oral cavity) have the same squamous tissue and biologic features, but their clinical presentation and responses to therapy differ according to site. In addition to this level of complexity, there is the inescapable fact that structures of the head and neck control essential, continuously operational functions: speech, swallowing, eating, and breathing. This fact means that the short-term and long-term side effects of treatment can profoundly affect the quality of life.

Even so, the management of locoregionally advanced head and neck cancer has undergone a profound shift during the past two decades. For advanced resectable tumors of the larynx, hypopharynx, and oropharynx, surgery has taken a back seat to organ-preserving strategies that retain speech and swallowing — chemoradiotherapy is now the standard of care for such cases. Moreover, radiotherapy is more intense than it used to be, and the addition of chemotherapy has made it even more aggressive.^{1,2} For patients with unresectable disease, the use of chemoradiotherapy has improved the three-year survival rate from a disheartening 15 to 20 percent to a more reasonable 35 to 50 percent. The results of recent studies involving more complex and intensive treatments, including sequential chemotherapy, show higher survival rates, near 60 to 70 percent.³⁻⁹

These advances have been achieved at a price, however. The treatment of severe toxic effects induced by aggressive therapy requires experienced caregivers and is time-consuming. One measure

of the toxicity of current therapies, severe mucositis, develops in almost two thirds of patients treated with chemoradiotherapy or hyperfractionated radiotherapy, and a considerable proportion of patients with this complication become dependent on feeding with gastric tubes.^{3,8,10} Severe side effects of aggressive therapy may be acceptable in patients with a grim prognosis. When the rate of survival among patients with advanced disease approaches 50 to 70 percent, however, the acceptability of severe long-term complications begins to change — yet sacrificing survival for less toxicity may not be a suitable alternative.¹¹

In this issue of the *Journal*, Bonner et al.¹² report on the phase 3 study of cetuximab, a monoclonal antibody against the epidermal growth factor receptor, plus radiotherapy for locoregionally advanced squamous-cell carcinoma of the head and neck. The results should be examined in the context of the current standards of care for patients with head and neck cancer. Bonner et al. found an unquestionable improvement in locoregional control, progression-free survival, and overall survival among patients treated with cetuximab plus radiotherapy, as compared with radiotherapy alone. Furthermore, and most surprisingly, the addition of cetuximab did not increase the incidence of severe mucositis. A gain in survival without a substantial increase in toxicity is a substantial gain that immediately draws the attention of clinicians. However, Bonner et al. did not compare the combination of cetuximab plus radiotherapy with the current standard of care — platinum-based chemoradiotherapy — and they did not administer the radiotherapy uniformly among all patients. These caveats

complicate the interpretation of the study's results.

How do clinicians decide whether to use cetuximab to treat head and neck cancer? Bonner et al. report a significant improvement in the median survival among patients in the radiotherapy-plus-cetuximab group, but this improvement does not tell the whole story. More important are the encouraging absolute and relative improvements in the three-year rate of survival: 10 percentage points and 22 percent, respectively. The benefit of cetuximab in terms of survival was evident for oropharyngeal cancer, the diagnosis in more than half the patients. In contrast, the use of the antibody did not improve the survival among patients with hypopharyngeal or laryngeal cancer.

Patients with oropharyngeal cancer also respond well to chemoradiotherapy. In a phase 3 European trial in which platinum-based chemoradiotherapy was compared with radiotherapy alone, patients with oropharyngeal cancer had absolute and relative improvements in the rate of survival of 20 percentage points and 70 percent, respectively, at three years.⁹ As a cautionary note in interpreting the early results of Bonner et al., the absolute and relative rates of survival in the European chemoradiotherapy trial had dropped from 20 percentage points and 70 percent at three years to 5 percentage points and 30 percent at five years.⁹ In another phase 3 study, the treatment of patients with very advanced hypopharyngeal and oropharyngeal cancers with platinum-based chemotherapy plus hyperfractionated radiotherapy was not associated with a significant improvement in survival.¹⁰ However, a subgroup analysis of data from that trial showed that patients with oropharyngeal cancer had a significant gain in survival from chemoradiotherapy.

In the study by Bonner et al., cetuximab appeared to be effective only when added to hyperfractionated radiotherapy, confirming that hyperfractionated radiotherapy should remain the standard of radiotherapy.^{2,3} But although treatment of the oropharynx and hypopharynx with hyperfractionated radiotherapy is effective, it is associated with a high rate of esophageal stenosis (25 percent).¹⁰ We do not know how many surviving patients in the trial by Bonner et al. remained dependent on food delivered by gastric tubes.

How do the results of the trial by Bonner et al. compare with those for the current North American standard of chemoradiotherapy with cisplatin? The seminal Intergroup study of patients with unresectable disease showed absolute and relative improvements in the three-year rate of survival of 14 percentage points and 70 percent, respectively, with cisplatin-based chemoradiotherapy.¹ The magnitude of this improvement was greater than that observed with radiotherapy plus cetuximab in the study by Bonner et al., but we acknowledge that these trials are not directly comparable.

The study by Bonner et al. shows a real benefit from adding cetuximab to radiotherapy. The long-term, absolute improvement has yet to be determined, however, and adding cetuximab had no effect on distant metastases. Moreover, the benefit from adding cetuximab to radiotherapy may be specific to particular sites of head and neck cancer and to the type of radiotherapy that is administered. Rather than administer platinum-based chemoradiotherapy, oncologists will be tempted to add cetuximab to radiotherapy or even to chemoradiotherapy, because these combinations are easier to administer and less toxic. However, despite the lack of comparative studies, oncologists should keep in mind that all studies of platinum-based chemoradiotherapy have shown greater improvement in patients than Bonner et al. found with cetuximab. Whether cetuximab plus radiotherapy is a better therapy than platinum-based chemoradiotherapy and whether cetuximab can be added to platinum-based chemoradiotherapy are important questions, the answers to which require randomized phase 3 studies. These are already under way. At present, for patients who can tolerate it, chemoradiotherapy with cisplatin remains the standard of care. Patients who cannot tolerate platinum-based chemotherapy for any of a variety of reasons should be expected to benefit from the addition of cetuximab to radiotherapy.

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Depressing Observations on the Use of Selective Serotonin-Reuptake Inhibitors during Pregnancy

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Persistent pulmonary hypertension of the newborn (PPHN) is a serious condition that typically occurs in full-term or near-term infants. Before birth, the fetus receives oxygenated blood from the placenta; a high pulmonary arterial pressure results in low blood flow to the lungs and shunting of the oxygenated blood to the systemic circulation through the foramen ovale and the ductus arteriosus. PPHN occurs when pulmonary arterial pressure remains high after birth and poorly oxygenated blood continues to be shunted to the systemic circulation. In one study involving 155 full-term newborns with moderately severe PPHN, 11 died, and nearly half the survivors had serious sequelae including cognitive delay, major neurologic abnormalities, and hearing loss.¹

In this issue of the *Journal*, Chambers et al. report a significant association between the use of selective serotonin-reuptake inhibitors (SSRIs) after the 20th week of pregnancy and PPHN in the offspring.² This is the latest in a series of

troubling reports of possible adverse effects of SSRIs on the fetus. The Food and Drug Administration (FDA) issued a warning in December 2005 stating that the use of paroxetine during the first trimester of pregnancy was associated with an increased risk of birth defects, particularly cardiac defects, as compared with the use of other SSRIs or no use of antidepressants.³ Health Canada⁴ has warned that the use of SSRIs and other antidepressants may result in a syndrome known as “poor neonatal adaptation,”^{5,6} which may include feeding problems, respiratory distress, jitteriness, and seizures.

Using a case-control design, Chambers et al. found that the infants of women who took SSRIs during the second half of pregnancy had five to six times the expected risk of the development of PPHN. PPHN is an uncommon condition (estimated incidence, 2 per 1000 live births),⁷ so even an increase in the risk by a factor of five or six would not result in a large number of cases. Chambers et al. estimate that PPHN occurs in