EDITORIALS

Adjuvant Nivolumab in Esophageal Cancer — A New Standard of Care

David H. Ilson, M.D., Ph.D.

Esophageal cancer is a leading cause of cancer-related illness and death throughout the world. Because there is no effective screening or early detection, most patients present with locally advanced or overt metastatic disease. Esophageal squamous-cell carcinoma is the most common histologic type worldwide in high-incidence areas such as East Asia, and adenocarcinoma is the dominant histologic type in the West.

A review of surgical outcomes in nearly 84,000 patients with esophageal squamous-cell cancer in 1980 indicated the daunting challenge of treating esophageal cancer.[1] Surgical exploration was performed in 58% of the patients, 39% underwent resection (30% died during or soon after surgery), 9% survived 2 years, and 4% survived 5 years. This sobering article formed the backdrop for subsequent studies of combined-modality therapy with preoperative chemotherapy or chemoradiotherapy. Improvements in and standardization of surgical technique, as well as improved postoperative care, have increased the safety and reduced the complications of esophagectomy.

Combined chemoradiotherapy alone or followed by surgery was established as a standard of care by the seminal Radiation Therapy Oncology Group (RTOG) 85-01[2] trial and the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS).[3] The combination of chemotherapy (carboplatin and paclitaxel) and radiotherapy for a short duration, followed by surgery, as described in the CROSS trial, is now the dominant practice in the United States, and it has advanced the field. However, the addition of more systemic chemotherapy to chemoradiotherapy preoperatively[4] or postoperatively[5] appears to have marginal to no benefit. Patients with a pathological complete response to chemoradiotherapy have increased survival. However, at surgery, most patients still have persistent disease — in particular, node-positive disease — that often recurs within the first year after surgery.

A modest advance has also been achieved with the use of the perioperative triplet chemotherapy regimen of fluorouracil, oxaliplatin, and docetaxel without radiotherapy.[6] In contrast, the previous use of perioperative cisplatin and fluorouracil has had marginal to negative results,[7,8] as have the addition of epirubicin and extension of the duration of preoperative therapy.[9]

A debate is ongoing about whether chemotherapy alone or combined chemoradiotherapy is the preferred treatment for esophageal cancer before surgery. Contemporary trials comparing these modern chemotherapeutic and radiotherapeutic approaches are ongoing to address this controversy (ESOPEC [Perioperative Chemotherapy Compared to Neoadjuvant Chemoradiation in Patients with Adenocarcinoma of the Esophagus], ClinicalTrials.gov number, NCT02509286; Neo-AEGIS [Neoadjuvant Trial in Adenocarcinoma of the Oesophagus and Oesophagogastric Junction International Study], NCT01726452; TOPGEAR [Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma], NCT01924819; and CRITICS-II [Multicentric Randomised Trial for Resectable Gastric Cancer], NCT02931890). Progress with combined-modality therapy has remained slow and incremental, with the recognition that most patients will die from locally recurrent or persistent disease or metastatic disease.

When added to chemotherapy or chemoradio-

therapy, targeted agents, including the vascular endothelial growth factor inhibitor bevacizumab, human epidermal growth factor receptor 2 (HER2)–targeting trastuzumab, and epidermal growth factor receptor–targeting cetuximab, have not increased survival. No clear, targetable biomarker has emerged in either squamous-cell carcinoma or adenocarcinoma.

Immune checkpoint inhibitors appear to be an active class of agents in both squamous-cell carcinoma and adenocarcinomas of the esophagus.[10] Activity appears to be highest in patients with microsatellite instability arising from mutations leading to DNA mismatch-repair protein deficiency, but this is seen in fewer than 1% of patients with esophageal cancer. Benefits of immune checkpoint inhibitors appear to be limited to patients with tumors that express programmed death ligand 1 (PD-L1), and nivolumab (irrespective of PD-L1 status) and pembrolizumab are currently approved for use as second-line or later therapy in patients with disease that is resistant to conventional chemotherapy. Trials have shown mixed results when immune checkpoint inhibitors are combined with first-line chemotherapy, with salient negative but some positive results.

In this issue of the *Journal*, Kelly et al.[11] report the results of CheckMate 577, a global trial involving patients with esophageal adenocarcinoma or squamous-cell carcinoma that had been treated with chemoradiotherapy and surgery. Resected specimens showed residual disease, and these patients were at high risk for recurrence. In this double-blind trial, patients were assigned to a 1-year course of adjuvant therapy with nivolumab or placebo. The trial showed improvement in the primary end point of disease-free survival, with a significant and clinically meaningful increase from a median of 11.0 months in the placebo group to 22.4 months in the nivolumab group (hazard ratio for disease progression or death, 0.69).

This benefit was observed across preplanned subgroups, with a greater benefit of nivolumab than placebo in patients with squamous-cell cancer (hazard ratio, 0.61) than for those with adenocarcinoma (hazard ratio, 0.75), a benefit in patients with node-negative disease (hazard ratio, 0.74) and node-positive disease (hazard ratio, 0.67), benefits across tumor stages (ypT0 hazard ratio, 0.35, ypT1 or ypT2 hazard ratio, 0.60, and ypT3 or ypT4 hazard ratio, 0.84 [the prefix yp denotes the pathological stage after neoadjuvant treatment]), benefits in patients with HER2-positive (hazard ratio, 0.78) and HER2-negative disease (hazard ratio, 0.69), and benefits in patients with tumors that were PD-L1–negative (hazard ratio, 0.73) and PD-L1–positive (hazard ratio, 0.75). Patients with tumors of the esophagus appeared to have greater benefit (hazard ratio, 0.61) than those with tumors of the gastroesophageal junction (hazard ratio, 0.87). No new safety signals were observed, and only 9% of the patients discontinued nivolumab because of treatment-related adverse events. Most important, a 1-year course of adjuvant nivolumab had no adverse effect on patient-reported quality of life.

CheckMate 577 is a practice-changing trial in the treatment of esophageal cancer. Although overall survival data are not mature, the doubling of median disease-free survival will almost certainly translate into an overall survival benefit. The trial shows the first true advance in the adjuvant therapy of esophageal cancer in recent years and will become a new standard of care. However, despite the improvement observed, most patients will not gain benefit from adjuvant therapy with nivolumab. More contemporary biomarkers, including the presence of persistent circulating tumor DNA after surgery, should be explored to better define high-risk populations and potentially monitor patients receiving adjuvant therapy.

Given the positive results with the use of nivolumab after chemoradiotherapy and surgery in patients with esophageal cancer, whether the adjuvant use of checkpoint inhibitor therapy may improve outcomes in patients undergoing definitive chemoradiotherapy without surgery is the subject of ongoing study (KEYNOTE-975, NCT04210115). Whether a benefit will be seen in patients undergoing perioperative chemotherapy without radiotherapy is also under investigation (KEYNOTE-585, NCT03221426).

Improvement in survival among patients with esophageal cancer has been long awaited in those undergoing the arduous journey of chemotherapy, radiation, and surgery. The CheckMate 577 trial provides a welcome new therapeutic option for these patients.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Breast and Imaging Center, Memorial Sloan Kettering Cancer Center, New York.

1. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma: I. A critical review of surgery. Br J Surg 1980;67:381-90.
2. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992;326:1593-8.
3. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
4. Ajani JA, Xiao L, Roth JA, et al. A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer. Ann Oncol 2013;24:2844-9.
5. Mokdad AA, Yopp AC, Polanco PM, et al. Adjuvant chemotherapy vs postoperative observation following preoperative chemoradiotherapy and resection in gastroesophageal cancer: a propensity score-matched analysis. JAMA Oncol 2018;4:31-8.
6. Al-Batran S-E, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019;393:1948-57.
7. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998;339:1979-84.
8. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 2009;27:5062-7.
9. Alderson D, Cunningham D, Nankivell M, et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. Lancet Oncol 2017;18:1249-60.
10. Smyth EC, Gambardella V, Cervantes A, Fleitas T. Checkpoint inhibitors for gastroesophageal cancers: dissecting heterogeneity to better understand their role in first line and adjuvant therapy. Ann Oncol 2021 February 17 (Epub ahead of print).
11. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med 2021;384:1191-203.

DOI: 10.1056/NEJMe2101983

Molecular Rescue in Pulmonary Arterial Hypertension

John H. Newman, M.D.

In this issue of the *Journal*, Humbert et al.[1] report on a new approach to the treatment of pulmonary arterial hypertension, particularly the idiopathic and heritable forms of the disease. The treatment, which is given subcutaneously every 3 weeks, is a fusion protein that impairs activation of one limb of the proproliferative transforming growth factor β (TGF-β) pathways. Why would inactivation of a TGF-β pathway be an effective approach? The answer is in the genes. Approximately 70 to 80% of cases of heritable pulmonary arterial hypertension and roughly 20 to 30% of cases of idiopathic pulmonary arterial hypertension are consequences of impaired TGF-β function in the pathway that involves bone morphogenetic protein (BMP) receptor type 2 (*BMPR2*).[2] Mutation and impairment of *BMPR2* may lead to a permissive function in other proproliferative and proinflammatory TGF-β pathways that may result in pulmonary vascular occlusion and fibrosis.[3] Therefore, it has been inferred that unmutated *BMPR2* acts as a "brake" on these disease pathways and that mutated *BMPR2* is ineffective in blocking them. Why *BMPR2* is involved in fibrosis and occlusion of small pulmonary arterioles in addition to bone function remains a mystery.[2,4]

The discovery of dysfunction of BMPR-II signaling in patients with pulmonary arterial hypertension led to the hypothesis that the receptor signaling could be "rescued" pharmacologically or could be rebalanced by suppressing other sites in the large family of TGF-β ligands and receptors.[5] This hypothesis is consistent with the early observation that the wild-type allele of *BMPR2* is an important determinant of net BMPR-II function when a variant is present on the second allele.[6] Although attempts at rescue or rebalancing of BMPR-II signaling have had mixed success, such measures have therapeutic potential and deserve to be pursued.[2,7] Many biologic approaches are under study; these include microRNAs, ligand enhancement with BMP9, blocking antibodies, and others.[4,8]

What is the nature of the fusion protein sotatercept? Sotatercept was designed to bind and trap the TGF-β family ligand activin[9]; it consists of the extracellular domain of the human activin receptor type II A fused to the Fc domain of human IgG1. The activin receptor is involved in hereditary hemorrhagic telangiectasia, which has an infrequent but well-known association with pulmonary arterial hypertension. The activin receptor in the fusion protein binds extracellular activin and prevents it from activating the native cellular activin receptor, thus trapping it. The Fc region appears to be a stabilizing portion of the protein.[10]