No Improvement in Palliation of Dysphagia in Esophageal Cancer by Addition of Chemotherapy

Written by Dennis Bittner

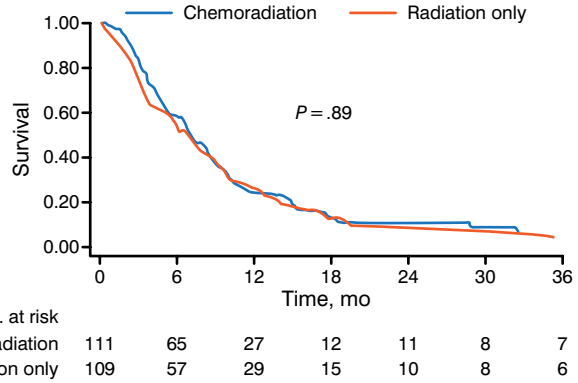
While much focus is on exciting advancements in the cure of cancer, there is a group of patients who cannot be cured and who need effective treatment with minimal toxicity for their predominant symptoms. In advanced esophageal cancer, 90% of patients have dysphagia as their predominant symptom. Although chemotherapy has demonstrated benefits in curing esophageal cancer, the only data on appropriate palliative treatment are from small, retrospective trials.

Michael G. Penniment, MD, MBA, Royal Adelaide Hospital, Adelaide, Australia, directed the Advanced Oesophageal Cancer Study to Compare Quality of Life and Palliation of Dysphagia [NCT00193882], the aims of which were to establish effective and minimally toxic treatments for relief of dysphagia in advanced esophageal cancer and to determine the effects of common cancer treatments on quality of life (QoL). The primary protocol end point of this randomized phase 3 trial was the relief of dysphagia, defined as improvement of ≥ 1 point on the 5-point Mellow scale for dysphagia 9 weeks after starting radiation therapy (RT) and maintained until week 13. A secondary end point was dysphagia progression-free survival (PFS), measured from randomization to the time of first progression of dysphagia, which was defined as an increase of ≥ 1 point on the Mellow scale, stricture requiring intervention, or death.

The 220 patients (median age, 65 years; range, 37–88 years) recruited for the study were nearly evenly divided between those from Australia and New Zealand and those from Canada and the United Kingdom. Of these, >80% were men and almost 70% presented with adenocarcinoma vs squamous cell carcinoma. Patients in Australia and New Zealand received RT of 35 Gy in 15 fractions, whereas those in Canada and the United Kingdom received 30 Gy in 10 fractions. The 111 patients randomized to chemotherapy received 5-fluorouracil 800 mg/m^2/day on days 1 to 4 and cisplatin at either 80 mg/m^2 IV at day 1 or 20 mg/m^2 on days 1 to 4. Toxicity was measuring using Common Terminology Criteria for Adverse Events v2, whereas QoL was graded using the OES-18 module of the European Organisation for Research and Treatment of Cancer QLQ30 questionnaire.

No statistically significant difference was seen in the 9-week dysphagia response or in the maintained response at week 13 between patients receiving RT alone and those receiving RT plus chemotherapy. There was also no significant difference between the 2 treatment arms for either dysphagia PFS or for overall survival (Figure 1). However, there was statistically significant increased toxicity (nausea and vomiting) in patients randomized to chemotherapy plus RT ($P<.01$). Despite increased toxicity, there was no significant difference between the arms on QoL analysis.

Figure 1. Overall Survival Comparing Radiotherapy With Chemoradiotherapy



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In summary, in Dr Penniment's assessment, this trial must be considered negative because there was no significant improvement in dysphagia when chemotherapy was added to RT, and the trial was not powered to show equivalence. In addition, chemotherapy added to the RT did not improve QoL compared with RT alone. He concluded that treatment with RT alone should remain the standard of care for palliation of dysphagia in patients with advanced esophageal cancer.

TRT in Addition to PCI Improves Outcomes for ES-SCLC

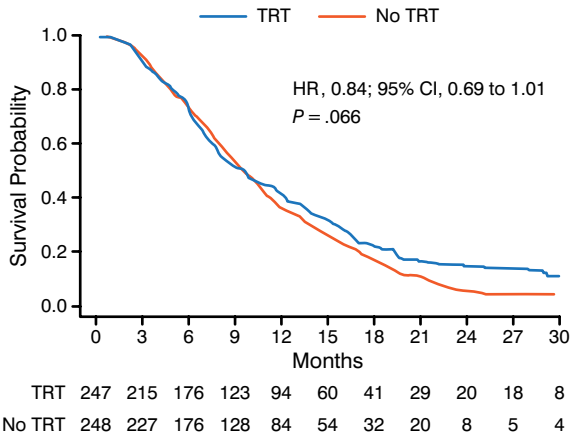
Written by Dennis Bittner

Prophylactic cranial irradiation (PCI) in the treatment of extensive-stage small cell lung cancer (ES-SCLC) has proven value in reducing symptomatic brain metastases and in improving overall survival (OS) at 1 year [Slotman B et al. *N Engl J Med*. 2007]. However, persistent intrathoracic disease occurs in 76% of such patients and intrathoracic disease progresses in almost 90% of this group. Ben J. Slotman, MD, PhD, Vrije Universiteit Medical Center, Amsterdam, The Netherlands, presented data from the Chest Radiotherapy Extensive Stage Trial [CREST; NTR1527] that evaluated the use of thoracic radiotherapy (TRT) in addition to PCI for treatment of ES-SCLC to prevent occurrence of thoracic disease and halt its progression.

Eligibility requirements for CREST were patients aged ≥ 18 years with ES-SCLS disease, who had a World Health Organization (WHO) performance status score of 0 to 2 and had shown either a complete response (CR), a partial response (PR), or a "good response" to 4 to 6 platinum-based chemotherapy treatments. Exclusions included any brain, leptomeningeal, or pleural metastases, and any previous brain radiotherapy or TRT. Patients were randomized and stratified by institute and presence or absence of intrathoracic disease, and then received PCI 2 to 7 weeks after chemotherapy and either TRT (10 fractions of 3 Gy) or no TRT. The primary end point of the study was OS, with secondary end points of progression-free survival (PFS), local control, failure pattern, and toxicity. The study was designed at 80% power to detect a hazard ratio of 0.76 for OS at 1 year (2-sided, with 5% significance). Accounting for a 5% dropout rate between randomization and start of treatment, 483 patients needed to be randomized. Accrual was successful, with 498 patients enrolled in 42 centers primarily in The Netherlands and the United Kingdom. The median patient age was 63 years, and 55% of participants were men and 45% were women. Over one-half of patients had a WHO performance status score of 1, whereas another one-third had WHO 0 and 10% had WHO 2 scores. In terms of their response to chemotherapy, just over 70% of patients had PR, one-fourth showed "good" response, and just 5% had a CR. As seen in other studies, nearly 90% of such patients with ES-SCLC treated with chemotherapy had persistent intrathoracic disease.

The primary end point was not met for OS because the hazard ratio did not meet criteria for statistical significance (HR, 0.84; 95% CI, 0.69 to 1.01; $P = .066$). However, in reviewing the OS curves, Dr Slotman said that the curves did begin to diverge in a statistically significant way at about 9 to 12 months in favor of TRT, and that the survival at 24 months was "highly statistically significant" ($P = .004$). Intrathoracic progression data showed strong statistical significance, with 43.7% of patients progressing who had received TRT compared with 79.8% for the control group ($P < .001$). Treatment was well tolerated, with all toxicities (cough, dysphagia, dyspnea, esophagitis, fatigue, insomnia, nausea/vomiting, and headache) with no difference between the arms and restricted to grade 3 on the Common Terminology Criteria for Adverse Events v3 scale. Dr Slotman concluded that TRT administered in addition to PCI for patients with ES-SCLC improved OS and PFS, and that TRT should be offered in addition to PCI to patients with a response to initial chemotherapy.

Figure 1. Overall Survival in CREST



CREST, Chest Radiotherapy Extensive Stage Trial; TRT, thoracic radiotherapy.
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Capecitabine Compared With Capecitabine Plus Oxaliplatin Chemoradiotherapy

Written by Emma Hitt Nichols, PhD

Preliminary findings demonstrate that patients with rectal cancer receiving radiotherapy with a combination of capecitabine and oxaliplatin have better local regional control compared with those receiving capecitabine plus radiotherapy. Hua Ren, MD, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China, presented interim data from the ongoing phase 3 open-label Adjuvant Treatment of Concurrent R and CAPOX or Capecitabine Alone for Stage II and III Rectal Cancer trial [NCT00714077].

The current postoperative therapy regimen for patients with advanced rectal cancer usually consists of radiotherapy and the chemotherapeutic agent capecitabine. It is unknown whether combination capecitabine and platinum-based chemotherapy has superior effects on clinical outcomes. This multicenter study assessed the efficacy and safety of these 2 chemoradiotherapy treatment regimens.

A total of 414 patients with rectal cancer were stratified by their pathologic stage (II or III) and randomized 1:1 to either the capecitabine (Cap) group (190 patients) or the capecitabine/oxaliplatin (CapOx) group (224 patients). Capecitabine was administered at 825 mg/m^2 alone (Cap) or at 825 mg/m^2 twice daily with 50 mg/m^2 oxaliplatin at the beginning of each week (CapOx). All patients underwent radiotherapy at 50 Gy in 25 fractions