Local Consolidative Therapy May Be Beneficial in Patients With Oligometastatic Non-Small Cell Lung Cancer

A new study suggests that it may be beneficial to offer local treatment (radiation or surgery) to patients with advanced non-small cell lung cancer (NSCLC) who have 3 or fewer metastatic lesions remaining after first-line systemic treatment (Lancet Oncol. 2016;17:1672-1682).

Because previous studies of the patterns of treatment failure in NSCLC have shown that it is more common to have disease progression at sites of prior disease as opposed to new sites, it is believed that perhaps more aggressive treatment of metastatic lesions would improve outcomes. The authors of the current study state that several previous retrospective and small prospective studies have shown that there may be a survival benefit to aggressive local therapy in patients with only a few sites of metastatic disease, but no well-controlled, randomized studies have been performed to date.

Daniel Gomez, MD, associate professor in the department of radiation oncology at The University of Texas MD Anderson Cancer Center in Houston and colleagues performed a multicenter, randomized phase 2 trial enrolling patients with stage IV NSCLC with 3 or fewer metastases who had received 4 or more cycles of platinum doublet chemotherapy or a tyrosine kinase inhibitor targeting epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) if an EGFR mutation or ALK rearrangement, respectively, was present in the tumor. Between November 2012 and January 2016, a total of 74 patients were enrolled either during or after receipt of first-line systemic treatment. The study was closed to accrual early because of a strong efficacy signal favoring the local consolidative therapy arm. In all, 49 patients were randomized and 25 patients were not eligible.

The patients in the local consolidative group were treated with the goal of ablating all remaining detectable disease with surgery, radiation, or a combination thereof as determined by the treating team. For the cohort randomized to systemic maintenance alone, the treating physician could choose among a set of standard options, including pemetrexed and bevacizumab, or a continuation of tyrosine kinase inhibitors in appropriate patients. Among this group, 13 patients had brain metastases. In 12 of these patients, the brain lesions were treated before randomization. The one patient with a small, asymptomatic brain metastasis responded to initial systemic treatment and was not treated further. Five patients in the local consolidative therapy group received systemic maintenance after the local therapy (3 patients with erlotinib, 1 patient with crizotinib, and 1 patient with pemetrexed).

Patients in the local consolidative group enjoyed significantly longer progression-free survival (PFS) versus those in the systemic maintenance-only group (11.9 months vs 3.9 months). The 1-year PFS rate was 48% in the local consolidative group.
and 20% in the systemic maintenance group. The marked PFS advantage led to early study closure. Overall survival data were not yet mature at the time of reporting. The time to the appearance of a new metastatic lesion was longer in the group receiving local consolidative therapy compared with those receiving systemic maintenance alone (11.9 months vs 5.7 months). No patients in either group had a grade 4 adverse event nor died from an adverse event.

“The take-home message is that in patients that met the criteria of the study, aggressive local therapy with surgery or radiation substantially improved progression-free survival compared to maintenance therapy or observation,” says Dr. Gomez. “The patients with stage IV lung cancer that were enrolled in the study met several criteria, including the following: 3 or less metastatic lesions, no progression after front-line chemotherapy, no malignant pleural effusion, and the ability to tolerate aggressive local treatment. The next step is to validate,” he adds.

“This paper reflects a growing sentiment and consensus in thoracic oncology,” says Mark Kris, MD, chair of thoracic oncology at Memorial Sloan Kettering Cancer Center in New York City. “It is not a new concept as several nonrandomized studies have shown benefit to this approach over the last 2 decades. The researchers performed a randomized study and that will make clinicians and patients more comfortable with the approach of consolidative local therapy. It is not a definitive study, but it is a good study of a growing trend in oncology.”

Clinical Implications
The authors of the current study say they believe theirs is the first randomized, controlled trial of its kind and that larger phase 3 trials are indicated to better define which patients are most likely to benefit. “There are planned expansion phase 3 studies,” says Dr. Gomez. “These trials will use overall survival as the primary endpoint (instead of progression-free survival), [will] enroll a larger number of patients, and [will] likely incorporate novel agents such as immunotherapy into the design.”

The observation that local consolidative therapy may increase the time to the appearance of new sites of disease suggests that it may change the natural history of the disease by conferring benefits beyond the local area treated. The authors recognize limitations to their study, including the relatively small size (however, this is due in part to the early closure based on the strong efficacy signal); imaging methods that differed due to insurance issues, which could affect the primary endpoint of PFS; and a diverse study population in terms of histologic and biomarker findings.

However, a major strength of the study was that it reflected real-world treatment approaches. “Patients with appropriate molecular alterations, such as in EGFR or ALK, were treated with molecularly targeted therapy rather than platinum doublet chemotherapy, which reflects clinical practice,” says Dr. Gomez. “Also, patients with brain metastases could be treated upfront with radiation or surgery, as is often done. The intent of this design was so that the treatment that was used in the trial did not vary substantially from oncologic practice, allowing for increased accrual and greater applicability of the findings.”

“As our systemic therapies improve, this study and the overall approach of consolidative local therapy will likely become more relevant,” says Dr. Kris. “The patients undergoing local therapy for oligometastatic disease had control of their systemic disease. The key is going to be proper patient selection so as not to subject patients to unhelpful and potentially harmful interventions.”

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