LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Can Unresectable Non–Small Cell Lung Cancer Become Resectable?

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H&O What is the definition of resectable disease in non–small cell lung cancer (NSCLC)?

JC The definition of resectable disease is based on the determination of the thoracic surgeon as to whether all the cancer that can be seen radiographically can be removed without excessive morbidity to the patient. The decision needs to account for the size and location of the disease as well as the characteristics of the patient, who must be medically fit enough to undergo the extent of resection necessary to remove the tumor and any involved lymph nodes.

H&O Can unresectable disease become resectable after chemotherapy or chemoradiotherapy?

JC The short answer is yes. The challenge is that we do not know at the outset which patients with disease that is unresectable initially will respond in a way that makes it resectable. For example, even if the patient has invasive disease that responds to treatment, will it shrink away from the major structure that made it unresectable at baseline?

Only one study has looked at preoperative chemotherapy or chemoradiotherapy in patients with historic stage IIIB NSCLC.[1] This was a small phase 2 study that was carried out with aggressive, highly skilled surgeons. A total of 46 patients with technically resectable, stage IIIB NSCLC based on the old staging system received 3 cycles of neoadjuvant platinum-based chemotherapy, followed by accelerated boost radiotherapy and definitive surgery. The investigators found that 35 patients were able to have surgery, and 27 patients had a complete resection. The event-free survival rate at 12 months was 54%. There were perioperative complications in 14 patients, including 2 deaths. These results certainly do not justify this approach without further studies.

> We will only be able to improve the cure rate if we can reliably predict who is going to be converted from unresectable to resectable disease, and we do not yet have this ability.

H&O What are the safety concerns regarding the use of surgery after chemoimmunotherapy?

JC Although there has been a lot of discussion about the safety of surgery after chemoimmunotherapy, large, randomized studies have not shown a meaningful difference between surgery after preoperative chemoimmunotherapy vs surgery after preoperative chemotherapy.[2] In addition, large studies have established the safety of

surgery after neoadjuvant chemoimmunotherapy, even with adjuvant immunotherapy.[3-6] A robust response to chemoimmunotherapy might lead to extensive fibrosis, which would make the surgery more challenging. Aside from that, there are no specific safety concerns as long as the patient had an appropriate post-treatment evaluation, including endocrine laboratory testing to look for thyroid dysfunction or adrenal insufficiency before anesthesia.

H&O What are the potential benefits of converting unresectable to resectable disease?

JC Although we now can use consolidation durvalumab (Imfinzi, AstraZeneca) in the unresectable setting, which has been a major game-changer, the progression-free survival (PFS) curves still are not good. Even with the addition of durvalumab to chemoradiation, the PFS rate in the phase 3 PACIFIC trial dropped from 45% at 2 years to 36% at 4 years and 33% at 5 years.[7] Just 1 out of 3 patients remaining alive and progression-free is not satisfactory. The numbers were even worse for patients who did not receive durvalumab, with a 5-year PFS rate of just 19%. The early data following neoadjuvant chemoimmunotherapy and surgery look much better than this. However, we will only be able to improve the cure rate if we can reliably predict who is going to be converted from unresectable to resectable disease, and we do not yet have this ability.

H&O Are there any ongoing studies that are looking at the conversion of unresectable to resectable disease?

JC The phase 2 MDT-BRIDGE study, which is planning to enroll approximately 140 patients with resectable or borderline resectable stage IIB to IIIB NSCLC, is looking at the multidisciplinary approach to giving patients preoperative chemoimmunotherapy, and then reassessing whether surgery or radiotherapy is appropriate (NCT05925530). Patients will receive neoadjuvant durvalumab and platinum-based chemotherapy, followed by either surgery and adjuvant durvalumab or chemoradiotherapy and consolidation durvalumab.

H&O What has been the effect of improved systemic therapy?

JC Improved systemic therapy has given us an increased ability to treat micrometastatic disease and potentially improve outcomes, so we are more enthusiastic about using a multidisciplinary approach to cure more patients than ever before. Surgery remains the curative mainstay, however.

H&O What questions remain to be answered?

JC Many questions remain unanswered. Notably, is there a population of patients with unresectable disease who can reliably be converted to resectable disease using specific preoperative regimens? This question will be almost impossible to answer. Another question is, do we negatively affect outcomes if our efforts to convert unresectable to resectable disease cause us to delay definitive radiotherapy? We need to make sure that the 5-year PFS rate is no lower than 33%. Until we know that we are not harming anyone with disease that remains unresectable by delaying radiotherapy, we should only offer induction therapy to patients with borderline resectable disease in the setting of a clinical trial.

H&O Is there anything that you would like to add?

JC The most important element of multidisciplinary patient care in the curative setting is a conversation between all the involved clinicians to make sure that we are all are on the same page, and that we are giving the patient the best chance for a cure.

Disclosures

Dr Chaft has provided contracted consulting for AstraZeneca, BMS, Genentech, Guardant Health, Janssen, Lilly, Regeneron, and Arcus Biosciences.

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