Editorial Commentary

Persistent N2 disease after neoadjuvant treatment...and now? —The oncologist view

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The role of surgery in stage III non-small cell lung cancer (NSCLC) remains a popular topic for controversy sessions during international conferences. Stage III is a wide definition, and includes tumors of various size and extent of lymphatic spread. Modern clinical trials in stage III disease focused on N2, to narrow the spectrum and increase the impact of clinical trials. Still, N2 includes a wide anatomical spectrum, ranging from single station, to multi-station or bulky disease. Many patients have comorbidities that affect tolerance of surgery, radiation and systemic therapy. For these reasons, treatment decisions remain highly individualized, with expertise and multidisciplinary tumor boards required to grant the highest possible quality standards.

What did we learn from the past? Based on pivotal clinical trials in France and Spain, showing the feasibility of neoadjuvant chemotherapy in N2 disease, this approach became popular in Europe in the 1990s. The Swiss Group for Clinical Cancer Research (SAKK) conducted its own trials, using a relatively intense chemotherapy regimen with 3 cycles of cisplatin 100 mg/m^2 and docetaxel 85 mg/m^2 as a backbone. In the nonrandomized phase II trial SAKK16/96, the overall clinical response rate (ORR) with chemotherapy was 66%, complete pathological remission (pCR) was 19%. Achieving R0-resection and nodal downstaging from N2 to N0-1 was associated with favorable prognosis, with a median overall survival (OS) and event free survival (EFS) of 33 and 14.8 months, respectively (1). The prognostic role of R0-resection and nodal downstaging was confirmed by many other groups in subsequent studies.

The randomized phase III trial SAKK16/00 studied the role of preoperative radiotherapy with 44 Gy in 22 fractions over 3 weeks in 232 patients with pathologically proven and operable N2-disease, using neoadjuvant chemotherapy in both groups. The rates of R0-resection (91% *vs.* 81%), nodal downstaging (64% *vs.* 53%) and pCR (16% *vs.* 12%) were slightly higher in the chemo-radiotherapy group. However, median EFS was approximately 12 months in both groups, showing no benefit for preoperative sequential chemo-radiotherapy over chemotherapy followed by surgery (2). Recently, the SAKK published a pooled analysis, showing 10-year OS rate of 29% in resectable N2 disease (3). Based on these results, in Switzerland, neoadjuvant chemotherapy followed by surgery is the standard for operable N2-disease, except for superior sulcus tumors, where neoadjuvant chemo-radiotherapy remains the standard of care (4). "Resectability" is based on the definition by the IASLC (International Association for the Study of Lung Cancer), which is implemented in all recent SAKK trial protocols (5). At our institution, we define resectability upfront, to avoid R1-2 resections in any patient with NSCLC. Outside of a clinical trial, we do not perform induction chemotherapy to "convert" unresectable tumors for surgery, because this concept was never proven to be effective in larger trials.

What do we do in persistent N2 disease? In our view, in the case of nonresponding, radiologically stable disease after chemotherapy, surgery is still an option, if the patient is fit, if lobectomy can be performed, and if there is no bulky or multi-level mediastinal involvement. We avoid (right-sided) pneumonectomy, because of increased morbidity and mortality (6). Based on the pathological analysis of

the resection specimen, and the postoperative condition of the patient, postoperative radiotherapy (PORT) should be discussed at the multidisciplinary tumor board, although the evidence supporting PORT is retrospective, as the results of the randomized LungART trial are pending (7). If the tumor progresses and becomes unresectable during chemotherapy, we dismiss surgery and switch to definitive chemo-radiotherapy. Before chemo-radiotherapy, we repeat PET-CT and brain MRI to rule our distant metastases. After chemo-radiotherapy, we do not use consolidation chemotherapy, but we routinely add consolidation immunotherapy, based on the results of the PACIFIC trial (8,9). In metastatic disease, optimal choice of further lines of systemic therapy will depend on molecular markers, which we test already at the time of initial diagnosis in stage III (and IV) nowadays.

What will the future bring? Relevant advances can be expected from neoadjuvant use of immune checkpoint inhibitors plus chemotherapy, a combination which is already very successful for the treatment of patients with metastatic NSCLC. In 2019, preliminary results in N2 disease were presented from the Spanish nonrandomized phase II trial NADIM. Patients with N2 or T4 N0 disease were treated with 3 cycles of nivolumab, paclitaxel and carboplatin. Among the first 41 operated patients, 83% had a major pathological response (MPR) and 59% had complete pathologic response, which is truly remarkable (10). Another trial recruited 30 patients with operable NSCLC, including 23 patients with stage IIIA, using neoadjuvant therapy with 2-4 cycles of atezolizumab, paclitaxel and carboplatin (11). Twenty-nine (97%) patients had surgery, 26 (87%) had R0 resection, and 57% had MPR. First results from the SAKK16/14 trial were released as an abstract (12). Sixty-eight patients with resectable N2 disease received 3 cycles of cisplatin and docetaxel, followed by 2 cycles of durvalumab. Fifty-five (81%) patients had surgery, the main reason for not undergoing surgery was disease progression. Radiologic response rate was 59%, EFS after 1 year was 73%. Further data, including pathological response rate, will be reported at the ASCO 2020 meeting. A new trial SAKK16/19 is ongoing, to study the role of low-dose radiotherapy as an immunosensitizer during neoadjuvant immuno-chemotherapy.

Perioperative immunotherapy remains work in progress. Safety needs to be addressed by randomized trials, although preliminary data from clinical trials do not suggest increased mortality or morbidity. The predictive value of pathological response for long-term survival needs to be validated. The hypothetical superiority of neoadjuvant immunotherapy over adjuvant immunotherapy warrants confirmation. Once the clinical benefit is fully established, the cost-efficacy of a short course of neoadjuvant immunotherapy will need to be compared with adjuvant immunotherapy for up to 1 year. Challenges will remain in the treatment of tumors progressing under neoadjuvant immunotherapy. Surgical trials provide laboratories with sufficient material, to get new insights into the biology of tumor escape mechanisms. These efforts will ultimately improve immunotherapy for NSCLC of all stages. Enrolment of patients into clinical trials therefore remains highly important.

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