The not so small role of adjuvant chemotherapy in resected non-small cell lung cancer

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In this retrospective study of 231 patients, Harada and colleagues evaluated real-world data on adjuvant chemotherapy in patients with stage I-IIIA non-small cell lung cancer (NSCLC) who underwent lobectomy or pneumonectomy plus lymph node dissection. The primary end point was overall survival (OS), while the secondary end points were recurrence-free survival (RFS) and safety/feasibility of cisplatin and vinorelbine. Eighty patients received adjuvant chemotherapy, 62 of whom (68%) received a cisplatin-based regimen and 18 (22%), a carboplatin-based regimen. In patients with stage-II NSCLC, adjuvant chemotherapy improved RFS and OS; however, in stage-III patients, only RFS showed statistically significant improvement.

We congratulate the authors for this well-conducted and designed retrospective study from a single center in Brazil. It reinforces the significant survival benefit of adjuvant cisplatin-based chemotherapy in patients with resected stage IB-IIIA NSCLC. We are all aware of the extensive body of literature evaluating adjuvant chemotherapy in NSCLC; however, most of the data come from large prospective, randomized clinical trials, where most of the patients enrolled are not reflective of our daily practice. Therefore, not infrequently, we extrapolate the results from a very limited and restricted population to a broader and heterogeneous group of patients. In this context, real-world data play an increasing role in health care decisions and help us fill some of the gaps in the literature. Although reports of adverse events in real-world data tend to be less accurate than the close monitoring of randomized trials, the former can still provide an idea of treatment tolerability and toxicity. In the study by Harada et al., 89% of the patients receiving cisplatin and vinorelbine had grade 3-4 toxicity, 49% were hospitalized due to toxicity, and 9% died. These numbers are alarming; nevertheless, the sample size was small (n = 62). Multiple studies have evaluated cisplatin combined with vinorelbine versus other cisplatin doublets and found a strikingly lower incidence of febrile neutropenia and neutropenia, with no difference in RFS or OS. In the United States, the standard adjuvant regimen is platinum-pemetrexed for non-squamous histology and platinum-docetaxel/gemcitabine for squamous cell histology.

After at least a decade of stagnation, the role of adjuvant treatment in resected NSCLC is finally taking important steps forward. The ADAURA trial recently reported an 80% reduction in the risk of recurrence or death with osimertinib compared to placebo in resected IB-IIIA NSCLC harboring EGFR-sensitve mutations. This led to the approval of this third-generation tyrosine kinase inhibitor (TKI) by the Food and Drug Administration (FDA) in the adjuvant setting. The survival data is still immature; however, due to its impressive improvement in DFS and central nervous system DFS compared to placebo, osimertinib quickly became widely adopted in the United States. Continuing to build on biomarker-driven adjuvant therapy, the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) (NCT02194738) is a large National Cancer Institute (NCI) sponsored National Clinical Trials Network (NCTN) initiative to address the role of genomic testing and personalized therapies in the adjuvant treatment of NSCLC. The study is evaluating crizotinib in resected IB-IIIA NSCLC with an ALK rearrangement and erlotinib in resected patients with EGFR-sensitve mutations. In light of the ADAURA study results, the enrollment in the erlotinib arm was recently suspended. The LIBRETTOO-432 (NCT 04819100) is a phase III study, which will enroll resected patients with IB-IIIA RET-fusion positive NSCLC to selpercatinib or placebo. Many more studies are on the way, and hopefully, the treatment paradigm will continue to evolve in the adjuvant setting.

There is a strong rationale for incorporating immunotherapy in early-stage NSCLC, given the breakthrough results with checkpoint inhibitors as monotherapy or combined with cytotoxic therapy in patients with metastatic disease. Immunotherapy has produced durable responses and impressive survival rates in advanced NSCLC. The ANVIL arm of the ALCHEMIST study randomized patients in more than 600 sites in the United States to nivolumab or observation after surgical resection and standard of care adjuvant therapy (chemotherapy if indicated) in resected IB-IIIA NSCLC. Primary end points are DFS and OS. The IMPower-010 is a phase III study, which randomized 1280 patients with resected IB-IIIA NSCLC to atezolizumab or best supportive care (BSC) after adjuvant chemotherapy. Atezolizumab showed a significant DFS benefit versus BSC in resected stage II-IIIA, with a more significant benefit in PD-L1 positive tumors. KEYNOTE-091 is another phase III trial randomizing 1177 patients with resected IB-IIIA NSCLC to pembrolizumab or BSC after adjuvant chemotherapy. The primary end point is DFS as well. There are multiple adjuvant immunotherapy trials currently underway, and we are eagerly awaiting the results. Table 1 summarizes the current immunotherapy and targeted adjuvant trials.

We have been seeing an overwhelming number of FDA-approved tyrosine kinase inhibitors (TKIs),
immunotherapies, and chemoimmunotherapy combinations in the late-stage setting of NSCLC. Unfortunately, and paradoxically, we haven't observed this progress in the early stages, where we are aiming for cure. With the approval of osimertinib and the possible role of adjuvant atezolizumab, we are finally starting to move the needle in this space. Besides the historic small benefit of adjuvant chemotherapy, reiterated by Harada and colleagues, cisplatin-based chemotherapy is still playing an important role as the backbone for most adjuvant TKI studies and for all the adjuvant immunotherapy trials. Therefore, selection of the least toxic adjuvant chemotherapy regimen will be even more important as we start to incorporate TKIs and checkpoint inhibitors in the adjuvant treatment of these patients. Based on the real-world data presented on adjuvant platinum-vinorelbine, this regimen should be discouraged in today’s practice. First, do no harm, right?

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