More Questions About Neoadjuvant Chemotherapy in Lung Cancer

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Despite all of its theoretical advantages, the use of induction chemotherapy is still considered experimental in the management of early-stage resectable NSCLC. In this comprehensive review by Gray and coauthors, the available data potentially supporting or refuting the use of chemotherapy perioperatively in lung cancer are well presented. A few additional points are worth commenting on.

Not the Same Populations!
When one compares the published meta-analysis of modern day induction and adjuvant chemotherapy trials, similar hazard ratios of just above 0.80 are seen with both strategies.[1,2] It is probably dangerous to conclude that these approaches have a similar efficacy, however, as the populations studied in induction trials are different from those in adjuvant studies. The most obvious difference is that induction trials rely on clinical staging to select patients, whereas adjuvant trials rely on pathologic staging: We all know that despite modern day imaging, including computed tomography–positron-emission tomography (CT-PET) staging, the concordance between clinical and pathologic staging is relatively poor.[3]

Another important difference is that in induction trials, all eligible patients at presentation are randomized to either get chemotherapy or not. In the postoperative setting, patients who have had a complicated or difficult recovery from their surgery are often not considered for adjuvant studies. The postoperative population attrition rate has been estimated to be around 25% (personal communication, D. Gandara).

Operative Risks After Induction Chemotherapy?
The potential increased risks of operating on patients who have received preoperative chemotherapy are often touted as a reason to avoid induction chemotherapy. This fear, however, is based entirely on retrospective single-institution series.[4,5] The authors rightly point to the fact that prospective, randomized phase III studies that have compared the strategies of surgery alone or after preoperative chemotherapy without radiation therapy have failed to show such an increment in operative risks.

Compliance to Systemic Chemotherapy
The optimal dose of perioperative chemotherapy has never been clearly established. Nevertheless, largely based on the experience in more advanced-stage disease, it is believed that a minimum of three cycles of chemotherapy should be the goal. One of the pitfalls of adjuvant or postoperative chemotherapy is the inability to give our patients the intended dose of chemotherapy. On trial, one-third to one-quarter of our patients are not receiving what most would consider adequate systemic therapy after surgery.

One of the theoretical advantages of a preoperative chemotherapy approach is better delivery of the systemic treatment. The phase III Chemotherapy for Early Stages Trial (Ch.E.S.T.) reported by Scagliotti at the 2007 annual meeting of the American Society of Clinical Oncology (ASCO) indeed documented that 99% of the patients in the preoperative chemotherapy arm received at least two of three cycles of cisplatin and vinorelbine and 85% received all three.[6]

The results of the Neoadjuvant/Adjuvant Taxol (paclitaxel) Carboplatin Hope (NATCH) trial were recently presented at ASCO 2009. The three-arm trial randomized patients to surgery alone, or surgery with induction or adjuvant carboplatin/paclitaxel chemotherapy. The investigators found a significant difference in the ability to deliver chemotherapy favoring the induction chemotherapy group: In an intent-to-treat analysis, 90% of the induction chemotherapy patients received all three cycles as planned, whereas only 66% of the patients in the adjuvant arm actually received any chemotherapy. Even if one eliminates from the adjuvant chemotherapy group those patients who...
died after surgery, as well as those who were found to have higher-stage disease or to be ineligible, only 74% of patients were able to get all three cycles.[7]

**Fewer Surgeries?**

Another theoretical advantage in favor of induction chemotherapy is the hope of performing fewer pneumonectomies as a result of tumor shrinkage with chemotherapy. The S9900 trial did not see such an effect; in fact, the pneumonectomy rates were identical in both arms of the study despite a clinical response rate of 41% and downstaging in the chemotherapy arm. Interestingly, however, the Ch.E.S.T. trial—with a reported lower clinical response rate of 35%—saw a dramatic decrease in the rate of pneumonectomies performed in the induction chemotherapy population (24% vs 10%). Further analysis may help identify reasons to explain this significant difference. One theory is that in the North American trial, many surgeons did not tailor their resections to the needs of the patient at the time of resection, but rather, to the patient’s needs at presentation.

**Tumor Molecular Analysis**

The field of tailored chemotherapy remains in its infancy in lung cancer, and the group from Tampa who authored this review is one of the leading North American teams researching this question.[8] At this technologic point in time, this is one area where the strategy of adjuvant chemotherapy has an edge over that of induction chemotherapy. The relative abundance of resected tissue certainly allows for more analysis than one can perform on the small biopsy specimens obtained before surgery. However, as the “sampling” technology improves, larger biopsy specimens will be available at diagnosis. At the same time, it is hoped that smaller tissue samples will be required for analysis, and possibly this theoretical advantage of “adjuvant decision-making” over induction will be lost.

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