Adjuvant Therapy for a 3.9-cm Adenocarcinoma of the Lung

PRESENTATION OF THE CASE

After routine staging tests, including a FDG-PET scan and MRI of the brain, a 59-year-old mother of four, never smoker, undergoes uncomplicated right lower lobectomy of the lung to remove a 3.9 cm adenocarcinoma with visceral pleural invasion (pIB, T2N0M0). Should she receive adjuvant chemotherapy? If so, what drug, dose, and schedule? *The Oncologist* 2013;18:1258–1261

PRO

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Despite successful surgery in this otherwise healthy middle-aged woman, recurrent lung cancer remains her highest risk for death. Five-year survival for stage IB (pT2aN0) lung cancer is 58% [1]. Barely more than half of patients who undergo a successful surgery, as this patient did, will be alive at 5 years. That is a sobering statistic, and anything that can improve this patient's chance for survival should be considered.

So, what about adjuvant chemotherapy? This patient with significant risk of recurrent lung cancer should not be denied adjuvant chemotherapy simply because her tumor measures 1 mm less than what is widely considered the cutoff for offering treatment. It is true that patients with higher stage of disease see more benefit with adjuvant chemotherapy; this has been borne out in all three of the large clinical trials that have shown a benefit with cisplatin-based adjuvant chemotherapy (International Adjuvant Lung Cancer Trial, or IALT [2]; JBR.10 [3]; Adjuvant Navelbine International Trialist Association [ANITA] [4]) and in a pooled meta-analysis of cisplatin-based studies [5]. Benefit is also seen with adjuvant chemotherapy in node-negative patients who have a large tumor. Although visceral pleural involvement itself would not be a trigger for adjuvant chemotherapy, the large size of her primary tumor would be. Multiple analyses have shown improvement in overall survival with adjuvant chemotherapy if tumor size is greater than or equal to 4 cm (Cancer and Leukemia Group B [6] and JBR.10 [7]). Notably, 5-year survival for patients with tumors 4 cm or larger was 59% in the observation arm and 79% with chemotherapy in JBR.10 [7]. A 3.9-cm tumor is, in my mind, close enough to 4 cm to fall within the rubric of deriving benefit from chemotherapy.

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CON

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It is difficult to argue against adjuvant chemotherapy for this patient because her risk of recurrence, and death, from this cancer is so terribly high. From the patient's perspective, one compelling reason to avoid cisplatin and vinorelbine would be to avoid toxic side effects. The potential for harm is real, whereas the potential for benefit may not be.

Survival projections based on the 7th edition staging criteria by the International Association for the Study of Lung Cancer estimate a terrifying 40% risk of death at 5 years for this patient [1]. The size of the tumor (<4 cm) decreases her risk somewhat among the stage IB subgroup (>3 to 5 cm); however, the visceral pleural invasion increases her risk by an equal proportion [2]. The facts that she is female and a never-smoker (both good prognostic factors) shave only a few percentage points off her risk [3]. This patient should be highly motivated to seek additional treatment.

Two clinical trials have demonstrated a reduction in the risk of death with four cycles of adjuvant cisplatin and vinorelbine, with a hazard ratio (HR) of about 0.80 [4, 5]; however, neither trial was able to demonstrate benefit specifically in the stage IB subgroup. Furthermore, a larger meta-analysis also failed to show statistical significance of the benefit in the stage IB subgroup, with a HR for four cycles of adjuvant cisplatin of only 0.93 [6]. On this slippery slope of subgroup analyses, much has been made of two individual retrospective analyses showing statistically significant benefit in the stage IB subgroup that is 4–5 cm [5, 7]. At 3.9 cm, this patient slips off the wrong side of this subgroup.

In other words, the benefit of adjuvant cisplatin-based chemotherapy for this particular patient, by strict criteria, may not be real; however, the potential for harm is quite real. There is the im-

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The choice of chemotherapy warrants some discussion. Although the most common regimen that has been studied is cisplatin combined with vinorelbine, as used in JBR.10 and ANITA, IALT allowed multiple other agents in combination with platinum, including vindesine, vinblastine, and etoposide, and the most common regimen in that trial was actually what we think of as an “old” regimen, cisplatin-etoposide. Ongoing clinical trials such as ECOG-1505 (ClinicalTrials.gov identifier NCT00324805) allow multiple different adjuvant chemotherapy backbones, including cisplatin-vinorelbine, cisplatin-docetaxel, cisplatin-gemcitabine, and cisplatin-pemetrexed. With the efficacy of pemetrexed in the nonsquamous setting in metastatic disease [8], earlier use of this agent in the adjuvant setting in patients with nonsquamous histology would be warranted. I would treat with cisplatin-pemetrexed in this case, given the efficacy of pemetrexed in the nonsquamous setting in advanced disease and the tolerability of this regimen.

Notably, the patient is a never-smoker and molecular testing for driver mutations such as *EGFR* and *ALK* would be of high interest. Whether adjuvant erlotinib in the setting of an *EGFR* mutation or adjuvant crizotinib in the setting of *ALK* translocation should be recommended is an unanswered question; randomized trials specifically targeting these populations have not yet been done, although several are planned. Interestingly, a phase II study of surgically resected patients with *EGFR* mutations who received adjuvant erlotinib for 2 years reported 2-year disease-free survival of 94% [9]. Enthusiasm for adjuvant tyrosine kinase inhibitors in this setting must be tempered by the results of several large trials that showed no benefit and perhaps a suggestion of harm. In a molecularly unselected population, Southwest Oncology Group’s SWOG 0023 trial showed a detriment to maintenance gefitinib in stage III disease after chemotherapy and radiation [10]. BR.19 was a phase III study randomly assigning molecularly unselected patients to either adjuvant gefitinib or placebo in stage IB–IIIA disease instead of or following adjuvant chemotherapy. This trial was closed after the results of SWOG 0023 were reported. Preliminary results of BR.19 showed no benefit to gefitinib and, in fact, a trend toward worse disease-free survival and overall survival; somewhat surprisingly, in the subset of *EGFR*-mutation-positive patients, overall survival was inferior with adjuvant gefitinib as well [11]. Although these studies have their flaws (e.g. nonmolecularly selected, premature closure, subset analyses of small numbers for *EGFR* mutation), their results lend credence to the position that adjuvant tyrosine kinase inhibitors should be given only in the setting of an appropriately targeted clinical trial. Enrollment in clinical trials attempting to definitively answer this question would be ideal if such driver mutations were found.

DISCLOSURES

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mediate risk of treatment-related death from neutropenic sepsis or metabolic derangement (1%–2%) and a risk of permanent hearing loss (3%), peripheral neuropathy (3%), and kidney damage (3%) [4, 8, 9]. The chemotherapy is unpleasant and debilitating, with a high likelihood of fatigue and nausea. Furthermore, vinorelbine is a vesicant and can cause peripheral vein irritation, which might require insertion of a central venous access device. Although there is a risk of death *during* therapy, a sobering finding from long-term follow-up of the International Adjuvant Lung Trial (the largest of the negative adjuvant trials), is that the risk of death from other causes was increased in the chemotherapy group (HR for nonlung cancer death: 1.34; (95% confidence interval: 0.99–1.81; $p = .06$), suggesting that patients were weakened in some way by the therapy and thus leading them to succumb to noncancer health problems at a higher rate, especially in long-term follow-up [10].

In summary, a reasonable patient could weigh the benefits and harms and be inclined not to take adjuvant cisplatin and vinorelbine. What’s more, for lack of prospective data, an enthusiastic medical oncologist lacks the moral authority to aggressively persuade her to agree to treatment if she is motivated by fear of toxicity. This case brings into sharp relief the vital need to develop more effective, less toxic adjuvant therapies for patients with resected lung cancer.

Platinum salts are the single most effective class of drugs for fighting non-small cell lung cancer in unselected patients, that is, patients not subclassified by molecular subtype. In the 1990s and into the modern era, cisplatin plus vinorelbine yields response rates of 20%–30%, a median progression-free interval of 4–5 months, and median overall survival of 8–12 months in patients with stage IV disease [11, 12]. With the discovery of *EGFR* mutation and targeted kinase inhibitors, selected patients with stage IV disease now have response rates of 70%–80%, a median progression-free interval of 9–12 months, and median overall survival of 24–31 months [13–15]. Furthermore, although they cause unpleasant side effects such as skin rash and diarrhea, *EGFR* tyrosine kinase inhibitors are, in general, far less dangerous than cytotoxic chemotherapy drugs.

The National Cancer Institute is launching a phase III study of adjuvant erlotinib for patients with resected lung cancer and *EGFR* mutation that will take 4 years to accrue. The primary endpoint will be overall survival, with results at least 7 years into the future. Clearly, advances in the treatment of stage IV disease will continue at a pace that will far outstrip our ability to test them in prospective clinical trials of adjuvant therapy. Meanwhile, we have retrospective data showing that the presence of *EGFR* mutation in resected lung tumors has more prognostic impact than age, gender, smoking status, and visceral pleural involvement, all of which are currently being used to parse therapy selection [16]. If it is reasonable to treat this patient with cisplatin plus vinorelbine based on available evidence, it is equally reasonable to test her resected tumor for the *EGFR* mutation and then search for clinical trial opportunities for her to consider.

If her tumor tests positive for *EGFR* mutation, the decision of whether to offer her adjuvant erlotinib, or afatinib, off protocol as an innovative adjuvant therapy is the topic for another essay. Whether you are for or against adjuvant chemotherapy for this patient, one thing is certain: It is more difficult to pre-

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scribe a therapy with only theoretical benefit when the therapy is toxic or costly. Given the revolution in medical care of patients with stage IV disease and *EGFR* mutation, it would appear the issue of cost may be the greater barrier to innovative use of EGFR tyrosine kinase inhibitors in the adjuvant setting, at least for the time being.

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