Sacrilegious Thoughts on Adjuvant Therapy for Resected Early Stage NSCLC

There’s a problem in our discussions of standard treatment for patients with higher risk resected early stage NSCLC, and that is that there is a pretty clearly defined standard of care of giving typically around 4 cycles of cisplatin-based chemotherapy to reduce the risk of recurrence, but in truth, the majority of people in the real world don’t get it. Still, I wouldn’t want to imply that the problem is definitely that doctors aren’t giving the right treatment to people who should definitely be getting it. I’m concerned that the problem may be that the well defined, trial-defined standard of care may truly not be the ideal choice for the majority of patients.

The median age of patients in all of the trials that give adjuvant chemotherapy is 59-63, which is a decade younger than the median age of a patient newly diagnosed with lung cancer in the US. Even looking at younger patients, a very substantial fraction have other medical problems or aren’t doing and feeling very well 4-7 weeks after a big lung surgery, which is when we’d usually want to give it. Many have kidney function that isn’t great, hearing loss, or some other good reason to not get cisplatin. So when we actually look at the treatments early stage NSCLC patients actually get, a huge fraction get no chemotherapy even if they would otherwise technically be a candidate based on the pathology findings, and the most commonly used regimen in the US is carboplatin/Taxol (paclitaxel), a regimen that has been tested as a post-operative therapy and failed to show a survival benefit, relegating carboplatin-based adjuvant chemotherapy to second tier status, below cisplatin-based chemo.

Last weekend, I gave a summary of some ASCO Highlights in lung cancer at a meeting for oncologists, and I was charged with reviewing some of the adjuvant therapy results from this year, including a trial called TREAT that Dr. Pinder covered in our own webinar on ASCO Highlights in Lung Cancer, and which asked the question of whether cisplatin/Alimta (pemetrexed) might be a regimen more feasible to administer than the most data-supported option of cisplatin/Navelbine (vinorelbine). The background of that trial is that the existing trials with the cisplatin/Navelbine regimen show that in some studies, more than half of the people came off of treatment before getting through it, and huge proportions of patients need to delay or stop treatment due to prohibitive drops in blood counts or some other toxicities, or they simply refuse to continue with more treatment. I’ve certainly seen this in many of my own patients, on or off of a clinical trial — even if they know that there is a potential survival benefit to be gained, some express that they’d rather be dead than to continue on cisplatin-based chemo. The trial actually confirmed that the cisplatin/Navelbine regimen as best studied is quite difficult to administer on any kind of regular schedule, at least without it being a soul-crushing experience; cisplatin/Alimta was more feasible, though not a cake walk itself either.

More concerning to me is the fact that, if you pool many of these older trials together, around 1% of patients die as a result of adjuvant therapy. Let me remind you that these are people who already have a significant chance of being cured. There is also some work from longer term follow-up in adjuvant therapy trials that suggests that the survival benefit from adjuvant...
Chemotherapy in the first few years may be compromised by higher death rates in recipients of chemotherapy more than 5 years out, compared with observed patients. Also of concern are the preliminary findings of the ongoing 1505 trial of cisplatin-based chemo with or without Avastin (bevacizumab) reveal that while there isn’t a statistically significant increase in serious side effects with addition of Avastin, the rate of treatment-related deaths on the two arms is 2.5% with chemo alone, and 3.8% with Avastin. [NOTE: Since writing this, I have learned from Dr. Suzanne Dahlberg, statistician for ECOG, that these numbers are not specifically attributed to treatment but could be from other causes, such as treatment-related recurrences. This is quite reassuring, as the quoted numbers were higher than I’d expect or hope to see for treatment-related deaths a multicenter North American experience.] So here are a few views on adjuvant therapy today that are from the perspective of an oncologist treating a broad range of patients in the community and noting that the experience from real world data differs from that of many of the studies we have available.

1) Cisplatin-based chemotherapy is the most evidence-based approach for improving survival, but the patient population in these trials is extremely cherry-picked and should actually be recognized as not being feasibly generalizable to all or perhaps even most patients with resected NSCLC.

2) The fact that many patients don’t receive adjuvant chemo, or if they do, they receive carboplatin-based chemo instead of cisplatin, isn’t clearly a failure to deliver the ideal treatment for that particular patient, but rather may be a very appropriate individualization for patients who don’t match the characteristics of the unusually young, fit, and motivated patients enrolled on the adjuvant therapy trials.

3) The adjuvant or neoadjuvant (pre-operative) chemotherapy trials with carboplatin-based regimens actually don’t suggest that they’re not active. They may possibly be less active, but a careful look suggests that they are largely underpowered and/or look at a population too unlikely to gain huge benefit from chemotherapy to be a fair test of the concept. I’m not sure that a solid carboplatin-based regimen wouldn’t perform just as well or better in the same population in a head to head trial, although we’ll probably never see that done. I think if the right trials were to be done, rather than have our data be limited by the vagaries of old trials with their own shortcomings, we’d find that some patients are very well served by carboplatin-based chemotherapy. I suspect it may be

4) We need to be very careful about the dangers of over-treating patients with more aggressive therapies than they can safely tolerate.

This isn’t meant to say that cisplatin-based chemo isn’t appropriate and shouldn’t be done for the right patient, but rather that I think it’s a mistake for oncologists or patients to feel a dogmatic pressure that cisplatin-based chemo is the ONLY answer for post-operative treatment for resected NSCLC, for every patient. Adjuvant chemotherapy actually harms some patients, but we don’t know enough yet to predict who those people are, just like the quote from advertising pioneer John Wanamaker: “Half my advertising is wasted: I just don’t know which half.”
We’re moving away from the “one size fits all” approach throughout cancer care, and I think we’re going to come to recognize that adjuvant chemotherapy for resected early stage NSCLC should be far more individualized, just as we should recognize that it’s a problem when the patients on clinical trials are too different from the patients in our own clinics to try to apply “square peg into round hole” practices.