How Should We Treat Frail Patients with Locally Advanced NSCLC?

Despite the fact that a very significant proportion of the “real world” patients have considerable medical problems such as markedly decreased lung function (pretty common with many years of smoking), weight loss (5 or 10% of body weight is usually considered a problem), or otherwise are not able to be very active. The vast majority of clinical trials for potentially curative, combined modality (chemo and radiation) approaches of chemotherapy and radiation have often been restricted to patients with a good performance status (PS), which means that patients are either unrestricted in their activities or are symptomatic but able to perform light work activities. Chemoradiation approaches, and especially those that include concurrent chemotherapy and thoracic radiation therapy (RT), are generally accompanied by considerable acute side effects and a treatment related death rate in the 5-6% range even in quite fit patients. With such challenges even for the healthier patients, this precluded those with marginal PS at baseline from participating in more rigorous multimodality strategies. So how should we manage patients with a PS of 2, corresponding to an ability to care for themselves but unable to work? The short answer is, we don’t have enough information to say, but there are a few studies that have addressed this very under-studied population.

One early study that demonstrated the feasibility of an attenuated concurrent chemoradiation approach in marginal patients not able to safely receive standard platinum-based chemotherapy and radiation was SWOG 9429 (abstract here). This multicenter, single arm study (everyone received the same treatment) accrued 60 “poor risk” patients, defined as having a PS of 2 with low blood protein levels or >10% weight loss, insufficient lung function reserves for more aggressive combined therapy (measured by the amount of air someone can blow out of their lungs in one second, called the FEV-1, for forced expiratory volume), or medical problems that made it infeasible to give standard cisplatin (including hearing loss, kidney problems, congestive heart failure, or peripheral neuropathy). The treatment approach included a relatively low dose of carboplatin IV on days 1 and 3, along with etoposide the first four days of a 28-day cycle. Chemo was given for a total of two cycles concurrent with daily chest radiation to 61 Gray (Gy) — a full dose. This trial demonstrated feasibility of this approach, with moderate acute toxicity and no treatment-related deaths, as well as encouraging efficacy: the median overall survival of 13 months, and the two-year survival was 21%; these numbers are in the ballpark of results from trials with more vigorous patients. Probably significantly, the majority of enrolled patients had a good PS and compromised pulmonary function, with only 18% of enrolled patients having a PS of 2.

A follow-up trial, SWOG 9712 (abstract here), evaluated the same poor risk population and tested the contribution of consolidation taxol every three weeks for three cycles, added after the concurrent chemoradiation approach from SWOG 9429 that is described above. The concept of consolidation taxol is based on the very encouraging results with consolidation taxotere with the SWOG trial 9504 (described in detail in a prior post), that had started shortly before SWOG 9712 (the first two digits signify the year the trial was developed). This study enrolled 87 patients, including 43% with a PS of 2 (a much higher proportion than in the earlier trial). Unlike the preceding trial, there were four treatment-related deaths during the concurrent
chemoradiation, and another four during the consolidation paclitaxel. The median survival was a less impressive 10.1 months, with a 25% two year survival. The investigators concluded that there was no evidence that consolidation paclitaxel improved survival, and there was also concern that it conferred prohibitive toxicity. However, an alternative explanation for the less favorable results in the later trial was that the now much larger subgroup of PS 2 patients could not tolerate this approach and may have contributed to the lack of benefit seen in the SWOG 9712 trial. In any event, there was no evidence of an improvement in OS from consolidation chemotherapy in poor risk patients with stage III, unresectable NSCLC.

Since we know that giving chemo and radiation concurrently increases cure rates but also the toxicity as treatment for stage III NSCLC, another idea has been to see if giving a less toxic targeted therapy as the systemic ("whole body") treatment could replace chemo during chest radiation to provide a similar systemic therapy benefit comparable to standard chemotherapy for poor risk patients with unresectable locally advanced NSCLC. Ready and colleagues (abstract here) reported on a treatment protocol for good and poor risk stage III patients, in which everyone started with induction carboplatin/paclitaxel for two cycles every three weeks, along with daily Iressa, the EGFR oral tyrosine kinase inhibitor. Investigators then continued Iressa along with concurrent chemoradiation for good PS patients and gave gefitinib alone without chemotherapy during definitive thoracic RT for PS 2 patients.

The trial closed early, based on the negative results of a high profile trial with Iressa (SWOG 0023, post here), in which maintenance gefitinib after concurrent chemoradiation was associated with a detrimental effect on OS in favorable PS stage III NSCLC (recent abstract with updated results in abstract here). A total of 20 patients on the poor PS stratum were enrolled, for whom the failure-free survival was 11.5 months, one year OS was 60%, and median OS 19.0 months. These efficacy results were pretty encouraging, and they were actually superior to those for the good PS patients, potentially because of a detrimental interaction of EGFR TKI therapy with concurrent chemotherapy (see prior post about why I have a strong aversion to this idea), or excessively aggressive treatment for the better PS patients, but the small numbers did not allow any significant conclusions to be drawn except that further study of EGFR inhibitor therapy combined with definitive RT in PS 2 patients is warranted. While studies of additional EGFR-based therapies, namely the monoclonal antibody against EGFR Erbitux, have been conducted in patients with a favorable PS (abstract here), subsequent trials have not yet been undertaken in a more marginal PS population.

I’ll come back to the point that we have very few studies to help us determine how to treat more frail patients with locally advanced NSCLC. It’s reasonable to do a sequential approach
of chemo followed by radiation or potentially radiation followed by chemo. We know that concurrent chemo and radiation leads to better long-term survival in healthier patients, but there is a real risk of major side effects and even dying from treatment, as the SWOG 9712 trial has shown us, despite the fact that this trial was developed for poor risk patients. The trials described above show that it’s feasible to treat with a lighter concurrent approach like carboplatin and etoposide or weekly platinum-based chemo with radiation (I’ve also used lower-dose weekly cisplatin and navelbine as an often extremely well-tolerated platinum doublet chemo that can be given with chest radiation, but I don’t have trial data to show on that). And the trial with Iressa gave a hint that perhaps targeted therapies could substitute for chemo during chest radiation to provide the systemic treatment coverage with lower toxicity overall.

While we don’t have answers, it’s good that we are finally developing the trials and asking the questions for the less vigorous patients who are out there, being treated by us in the clinics based on our best judgment but little real information to guide us. I hope to include more definitive conclusions over the coming years, as this poorer performance status patient population finally gets a greater share of attention in our clinical trials.