Updates on Mono and Combination Therapy

This study by Bendstrup and colleagues looked to evaluate the effects of nintedanib in patients with IPF based on their comorbidity index. Now, given the common occurrence of comorbidities in patients diagnosed with IPF, the authors of the study aimed to assess the effects of nintedanib in patients with IPF subgroups based on their comorbidity burden.

They pulled data from five clinical trials in which patients were randomized to either nintedanib or placebo, which included the tomorrow trial, the two-phase, three impulses trials, the end mark trial, and another phase three trial. The comorbidity burden was assessed using the Charleson Comorbidity Index, which is a validated scoring system that takes into account 19 different co-morbidities to predict a 10-year mortality. They then divided the patients into two subgroups, those with a CCI score of less than or equal to three, and those with a score greater than three. For reference, a CCI score of four predicts an estimated 10-year survival of about 53%.

The authors observed no significant difference between the subgroups and the rate of FVC decline. And although patients with a comorbidity index score greater than three had numerically worse than St George's Respiratory Questionnaire score, there was no statistically significant difference between the subgroups. There was additionally no significant difference in the time to first exacerbation of IPF or the time to death.

The adverse event profile was actually similar in both subgroups, although the proportion of patients who discontinued drug due to adverse events was greater in the group with a higher CCI score. Series adverse events were reported more frequently in patients with a CCI score greater than three in both the OFEV and the placebo groups.

Overall, this study demonstrates that nintedanib is effective in reducing the rate of FVC decline regardless of comorbidity index score. But that patients with a high comorbidity index are at increased risk for drug discontinuation. Using the CCI score may enable providers to identify patients at high risk of adverse events and drug discontinuation, and thus increasing vigilance in monitoring and addressing for possible side effects early. It's clear that regardless of comorbidities, patients with IPF benefit from antifibrotic therapy, and it's imperative that clinicians remain proactive in managing adverse events as to prevent early drug discontinuation.

This actually is an interesting and important study done actually in Japan. And what the issue is that many patients who are on antifibrotic treatment with pirfenidone or nintedanib are on those standard treatment these days for patients with idiopathic pulmonary fibrosis, but some patients actually deteriorate. And the question that has come up in people's mind, both patients and physician, what if we do a combination therapy with nintedanib and pirfenidone, and is it safe?

And that was basically the object of this study done in Japan, where the safety and the tolerability of combination therapy with nintedanib and pirfenidone for idiopathic pulmonary fibrosis was done. Now, this was a multi-centered retrospective observational study. So therefore, this is an observational study retrospectively based on database in their centers. So there is a lot of selection bias and those limitations of this particular study.

That said, the combination of nintedanib and pirfenidone when used in patients who were deteriorating, and this combination was the mean duration of monotherapy before the start of the therapy of combination were about eight to 26 days. So these patients were all advanced disease, and they had been receiving either pirfenidone or nintedanib monotherapy for about 800 day. And then the failure of combination therapy was assessed over 322 days.

So in a small number of patients, 34 and 17 patients had continued combined treatment more than 26 and 52 weeks. And the bottom line of this is that the third study, retrospective observational study, the combination therapy has tolerable safety and profile in this selected small number of patients in Japan.

Now, there is always a concern about side effects when you are having patients take two drugs that have a similar side effect profile. And one of the side effect profile is liver function toxicity. Even though the liver function toxicity in patients receiving nintedanib or pirfenidone is a relatively small, like about one or 3% of patients who receive individually, the combination therapy had about 4%, meaning two of this small number of patients had liver function test abnormalities that was significant.

So that would give about a 4% likelihood, at least in the retrospective study, of the liver function test abnormalities. And another patient had a lung collapse. So this combination therapy overall suggests that it is safe, but it then warrants a prospective, well-designed study to see if the combination therapy is worthwhile to try for patients with idiopathic pulmonary fibrosis who have failed monotherapy. And that's basically the summary of this particular interesting study using a combination therapy of nintedanib and pirfenidone in idiopathic pulmonary fibrosis. Again, a study short study, small study, sample size more in Japan.

Well, I cannot really draw meaningful conclusion in this small number of patients, so this is a time to look into prospective studies. So I cannot tell that it's relatively safe to try, but I would caution the patients receiving these medications in the real world experiential. I would alert the patients that you would want to be monitored very carefully by experienced investigators or clinicians familiar with the side effects, especially the liver toxicity.

So I would alert the community physicians to be a little bit on the cautious side and be on the alert side for toxicity, that there is no real data to convincingly say it is safe that we can go ahead and try it. So that's my caution about it.