Does Immunotherapy Work in Patients with Driver Mutations like EGFR and ALK?

Presented by H. Jack West, MD
Medical Director, Thoracic Oncology Program
Swedish Cancer Institute
President & CEO

TRANSCRIPT

A significant minority of our patients with advanced non-small cell lung cancer have a tumor that harbors what we call a driver mutation which is a single mutation in the DNA that is responsible for the growth and cell division of the cancer. Because it alone is the big driver of the cancer, if you have a targeted therapy that can hit it and inhibit this mutation you can really bring the cancer to its knees. These are oral targeted therapies that are generally as much as possible our first treatment approach for these patients.

Of course, one of the other treatment approaches that we all hear about on television commercials or in the news is immunotherapy. This concept of giving an IV medication that can help stimulate the immune system to better recognize and attack the cancer at least in some patients. We've been excited about testing this in all sorts of patients, but some patients respond better than others. One of the early themes from the first few years of using these immune therapies in patients with advanced non-small cell lung cancer has been that they don't seem to work very well in patients with driver mutations like EGFR or ALK. We began looking at these patients as a subset of the trails of chemotherapy compared to immune therapy as a second-line treatment in patients who have already been on chemo. In those studies, all the other patients seemed to do better with immune therapy but patients at least with EGFR mutations have tended to not do any better with the immune therapy than with chemotherapy with a drug like Taxotere. Our general observations about treating patients with an ALK rearrangement, a very similar concept, have really shown that we rarely see patients who get a good response to these immunotherapies as a single drug.

That has been our general conclusion, that these drugs simply don't seem to work. Except, we've seen some new data to suggest that we may need to change that interpretation at least if we're giving this in a different context and giving immune therapy combined with chemotherapy and maybe a drug like Avastin which blocks the tumor blood supply. This drug is also known as bevacizumab.

A trial called IMpower150 was generally meant as a first-line treatment for patients with advanced non-small cell lung cancer that was non-squamous subtype. This trial was largely for patients who didn't have an EGFR mutation or ALK rearrangement. It gave patients chemotherapy combined with Avastin as the standard treatment. Another arm of the trial gave them chemotherapy with Avastin and an immune therapy called Tecentriq and in a third arm of the trial tested chemotherapy with Tecentriq but didn't include the Avastin. Importantly in this trial patients who had an EGFR mutation or an ALK rearrangement were allowed to go on the study as long as they had already received treatment, a pill against their specific mutation, and their cancer had progressed on it. So, they had kind of run out of options against that specific mutation and now needed to pursue chemo-based treatment. This study showed that in the broad population there was an improvement in overall survival for patients in the trial all together. It also showed that there was an improvement in the overall survival of the patients even if they had an EGFR mutation or an ALK rearrangement. In patients who have one of these mutations, there was also improvement in the progression-free survival - the time before the cancer began to grow on treatment. So, if you were on this four-drug combination of carboplatin and Taxol chemotherapy with Avastin and Tecentriq you have the best progression-free survival and overall survival even if you have an EGFR mutation or an ALK rearrangement with the results particularly good for the patients with an EGFR mutation. Interestingly and importantly, in the third arm of the study that was with chemotherapy and the immune therapy Tecentriq but didn't include the Avastin, there wasn't the benefit that we saw compared to the four-drug combination. So, the Avastin may be a significant contributor here.

We don't know whether other combinations of chemo and immune therapy will be effective for patients with an EGFR mutation or ALK rearrangement because the patients with these driver mutations have not been included in these trials in other settings because they've really focused these patients onto the pill-based therapies as a first treatment. But there are a new batch of trials that are beginning and getting going to really carefully explore if the patients with an EGFR mutation or ALK rearrangement can benefit from immune therapies of all different kinds and combinations at least if given after they have completed their pill-based therapy. This is work in progress and there was even another drug called Durvalumab or Imfinzi that has shown some activity even as a single drug in some patients with an EGFR mutation at least if those patients have high levels of the PD-L1 protein.

This is an evolving story, but the conclusion is that we were too early to conclude that these immunotherapy drugs do not work in patients with EGFR mutations or ALK rearrangements particularly in the patients with EGFR mutations. It seems that their best use is probably in a combination with chemotherapy that may need to be given with Avastin. We really need to learn more, and we will because there are many studies looking at this.

https://www.youtube.com/watch?v=zwmXtqeOIgQ&feature=youtu.be