Drawing the map: molecular characterisation of NSCLC

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Disclosures

These are my disclosures.

Learning Objective

These are the learning objectives, so after the presentation you will know how to identify the molecular pathways that drive malignancies, the importance of genetic testing in approving diagnosis and identifying opportunities for treatment, and recognise the limited options we have for squamous cell non-small cell lung cancer.

Question 1

There is no right or wrong answer here, but the question to start with is: should molecular profiling be part of the diagnostic workup in a patient with advanced squamous NSCLC? Smoking, squamous cell, non-squamous cell, lung cancer. Can you please vote? OK, so half of you said yes, and half of you said no. I think it is interesting in the discussion to learn more about why this is so balanced.

First-line therapy with gefitinib prolongs PFS in patients with *EGFR* mutation

This is a study published 8 years ago about when we learned why the *EGFR* mutation testing was important. This is a study where patients were treated either with gefitinib, so a first generation TKI inhibitor or chemotherapy, and what we saw in this curve was that there was a crossing of the survival curves, and in general, the crossing of survival curve means that there are two separate populations present.

As you know, when further identifying this group, there was identified a population of patients who were *EGFR*-mutation positive, and these patients did better on the first generation TKI than on the chemotherapy. That was the opposite in the *EGFR*-mutation negative patients or the *EGFR*-mutation patients did better on chemotherapy than on the first generation TKI.

ESMO Guidelines 2016

That led to the following guideline and this is the example in the non-squamous. This is the ESMO Guideline of 2016. In Stage IV NSCLC, we first do molecular testing and in

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cases of EGFR-positive, we start on an EGFR-directed therapy, and in case of ALK translocation-positive, we start on ALK-specific treatments.

In case that is not present, you have chemo with the chemotherapy which other speakers will talk about.

Crizotinib as first-line therapy prolonged PFS in patients with advanced ALK-positive NSCLC

This is the study, and there was an update of another study this morning, but this is just to show that for the ALK, it is seen that a specific ALK inhibitor out performs chemotherapy, and that is why also in there was the advice to test for ALK in the guidelines.

Tumour responses to crizotinib in ROS1-rearranged NSCLC

What we are learning more and more, and this is just one example from the ROS1, so when patients can have a ROS1 rearranged NSCLC, and then it was also shown that these respond to the drug, crizotinib, and there were a higher number of responses and durable responses, so we are learning more and more about all these specific genetic abnormalities in lung cancer.

Case discussion

This is a case who was referred to our hospital and there were no further treatment options for this patient. He came to us and asked whether we really didn't have any options. It was a 65-year old male who had an adenocarcinoma of the right upper lobe with liver and left adrenal gland metastases, who was tested in the local hospital, EGFR-negative. There was no ALK translocation, and he started in 2013 on cisplatin pemetrexed with partial response, continued on maintenance treatment, but then developed progressive disease after eight cycles.

Case (continued)

Then he started on docetaxel as a second-line treatment, but he was hospitalised due to a cardiac arrest after the second cycle, and they discontinued the docetaxel.

Question 2

Then the patient came to me, and the question to you now is what should you do? Well, indeed there are no further options. I will remind you this was 2013, so I remind you that at that time there was no immunotherapy, but for the question we have it in there, so best supportive care, restart on another chemotherapy, check for the mutation status,

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consider sending the patient for a phase 1 study, or immunotherapy, either with or without PD-L1 testing.

Please vote. Most of you decided to start on the immunotherapy and one-third would check the mutation testing. That indeed is what we did. In the referring hospital, they only checked for certain exons in the *EGFR* domain, only 19 and 21, and we re-examined the biopsy using next generation sequencing, and we found out that the patient was exon 18 positive for the *EGFR* mutation, so we started him in 2014 on erlotinib, 150mg daily, and he again had a partial response, but as we know also these *EGFR*-mutation positive patients get a recurrence and it took him 2 years to get progressive disease again in the liver and the lung.

Question 3

The question now is what would be your next step? Start him now on immunotherapy, restart the chemotherapy, best supportive care or do a new mutation testing? OK, so half of you would do new mutation testing, and the other ones would shift him now to immunotherapy.

Case (continued)

We did a new mutation testing, so we took a biopsy from the liver and also took a liquid biopsy which was at that time experimental in our hospital, but for cfDNA, both of these tested positive for the T790M. There is a drug available for that, osimertinib, so we started him on osimertinib, 89mg/day, and he is now, almost 2 years later, still in a partial response, so this shows the options we have now in these mutated genetically changed patients.

Osimertinib versus platinum + pemetrexed in T790M-positive advanced NSCLC: PFS

The fact that osimertinib is chosen above the chemotherapy is based on this trial. This is a trial in the T790M-positive NSCLC patients where it was shown that osimertinib outperformed in chemotherapy in progression-free survival.

I will come back to the issue of immunotherapy a bit later.

Follow up targeted therapy: gefitinib in EGFR-positive patients

That changes our field on the overall survival a bit. As you may recall from the first study on the first-line EDFR TKIs compared to chemotherapy, we did find a difference in the progression-free survival, but at the end the overall survival was no different, and it was due to the crossover, for instance. But now we know that when we have the T790M-positivity

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after the first generation TKI, we can still expand, so this will translate into an overall survival in time.

Acquired resistance also develops

We know that also with the ALK, there is the occurrence of resistance, so these tumours are dependent on this driver mutation, and when you block that driver with some kind of drug, they will develop changes or develop new mutations in that domain so that the tumour will start growing again. This is a very – I'm not going into detail – but this is a very interesting patient with an ALK where ultimately, every time, they did new mutation testing to see that there were new mutations or changes in the ALK which led to a new treatment and ultimately, this led to outgrowth of clones or new mutations which were treatable again.

Performing NGS for a more comprehensive molecular screening

The other thing is that the next generation sequencing, when you do that you get more and more drivers. We heard just this morning about the beneficial effect of *BRAF*, the therapy and the discussion about that, that it could be first-line treatment now also. This is, when we are going to test patients, we are going to find more and more mutations, the *BRAF* in 2%, *HER2* and all the other mutations. Some of them are not targetable, as you know, for the *KRAS* at this moment, but still you will find mutations which can lead to a more targeted treatment.

Survival of patients with drivers: targeted therapy versus no targeted therapy

And that's important. This is from a very elegant study in my view where they looked at patients who were having a genetic abnormality, so they had some kind of oncogenic driver, and then they looked at whether these patients were treated with a targeted therapy or without.

What you can see here is that when the patients are treated with the targeted therapy, they do better, but when they are not treated at any time with the targeted agent, they do just as good as patients without a drug. That shows the importance of when you have to identify the driver and also start the specific therapy for that.

Oncogenic drivers in NSCLC

And then we got into the problem of do we need all these phase 3 studies to show that this is really effective? This is from an article in the *British Medical Journal* of 10 years ago. This is about the evidence for a parachute, and it also said that there's never been a

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randomised study showing that the parachute is effective, and still we are using it. So, probably for some things we don't need all these randomised studies.

Second-line nivolumab in non-squamous NSCLC: OS by subgroup

This is coming back to the issue of immunotherapy in an *EGFR*-mutated patient. In first- and second-line, that is not a good option at this point, and that is based on a subgroup analysis – this is from the nivolumab, but there are other studies showing the same thing, that in a patient who is EGFR-positive, immunotherapy may not be that effective. It shows that in the *EGFR*-mutated but also in other oncogenic driver patients that we see, these patients seem to do less well on immunotherapy, so it's more important that you try to identify the target and treat them with the targeted agent than you shift into immunotherapy.

We know – and that's the other thing – that during the course of treatment when you have first generation or second, and then you have the third generation TKI for EGFR like osimertinib, that ultimately you end up with your possibilities, as we are now, and then the tumour may also have heterogenically changed in the sense that then immunotherapy may be an option. But in this patient, as a secondline treatment, or say a second-line EGFR treatment, that would not be the best option, and here osimertinib was the best option to choose.

What about squamous cell carcinoma?

To end, what about squamous cell carcinoma? Now, we know that in the squamous cell carcinoma, the percentage of targetable mutated patients is far lower, so when you look into the incidents of EGFR- or ALK-positive squamous cell lung cancer, it's less than 5%.

ESMO Guidelines 2016

That is also in the guidelines. In the ESMO Guidelines, it states that the patient with the squamous cell lung cancer in whom are never or light smokers, so maybe the strange squamous cell patient, that you could do the molecular testing. I think the fact that half of you choose to do the testing in every patient in something which we can debate on, whether you follow this or that you have the resources to do mutational testing in every patient. But the incidents which you will find when you test every patient will be very low.

Conclusion

To conclude on that, I think that molecular profiling has increase the therapeutic potential in advanced NSCLC, and for the majority of patients, certainly for those with squamous cell lung cancer, targetable drivers are lacking.

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