Scott Edwards:

Hi, welcome to the education session on the strategies for managing patients receiving MET TKIs. I am Scott Edwards, and I'm an Oncology Pharmacist from St. John's Newfoundland. This is my disclosure slide.

In the presentation today, we will review the safety profile for MET TKIs. We will provide some detailed recommendations for management of peripheral edema, which is a really common side effect of MET TKIs. And we will also review other toxicities from these agents, as well as review the practical implications of using MET TKIs.

First of all, let's review the safety profile for MET TKIs. The treatment for patients with metastatic non-small cell lung carcinoma has historically consisted of systemic chemotherapy. An improved understanding of the molecular pathways that drive malignancy in non-small lung carcinoma has led to the developments of agents that target specific molecular pathways.

As you can see from the pie chart, multiple targeted molecular alterations have been identified in non-small cell lung carcinoma, including the MET receptor. MET Exon 14 skipping mutations account for approximately three percent of non-small cell lung carcinoma cases. In Canada, there are two approved MET Exon 14 skipping therapies, tepotinib and capmatinib, which are both oral ATP competitive, highly selective, type 1b MET inhibitors. These agents inhibit hepatocyte growth factor receptor tyrosine kinase. These agents block the MET pathway, causing decreased cell proliferation, survival, and metastases.

Patients with MET Exon 14 skipping mutations tend to be older than patients with other oncogenic drivers. Therefore, as clinicians, we should consider the more complex management needs of these patients.

This slide highlights the toxicities of the MET TKIs. And you can see from the slide that the toxicity profile for both of these agents is very similar.

There are potentially serious toxicities that can occur with these agents, and these include interstitial lung disease, pneumonitis, hepatotoxicity. And these drugs can cause embryo and fetal toxicity, so we must evaluate pregnancy status prior to use in patients who may become pregnant.

The most common side effects are listed here on the slide, and they include peripheral edema, GI toxicities, dyspnea, increase in creatinine, and fatigue.

Rates of permanent discontinuations are 16 percent for capmatinib and 20 percent for tepotinib.

We will now discuss in more detail these five toxicities that occur with the MET TKIs. We will evaluate the frequency, monitoring, and management of each one of these toxicities.

Peripheral edema is the most common toxicity, and we will evaluate this toxicity first.

Mild to moderate peripheral edema is a common class effect of MET TKIs. As you can see from the slide, peripheral edema happens for all grades at about 50 percent for capmatinib and 63 percent for tepotinib, and grades 3 or higher at 11 percent for capmatinib and 3.7 percent for tepotinib. So, it's quite a common toxicity for these agents.

And as you can imagine, this peripheral edema has a negative impact on the patient's quality of life. Some of the symptoms the patient may experience are pain, limb swelling, heaviness, and just an overall impairment of their well-being. The picture on the right shows a grade 2 bilateral edema of the hands in a patient receiving tepotinib. And this picture is a good representation of the type of symptoms a patient gets with MET TKI-induced peripheral edema.

It is really important as oncology clinicians that we appropriately manage peripheral edema in patients on MET TKIs. This slide highlights the appropriate steps for management: prevention, early recognition, and prompt intervention. We will go over each one of these steps.

In contrast to the onset of most treatment-related adverse events, edema appears to be a cumulative toxicity with a delay in onset. Time to onset has been reported at approximately 8 weeks for tepotinib, 3.5 to 5 months for capmatinib. It is important, though, that we stress to patients the importance of being proactive from the start of therapy.

Prevention techniques like limb elevation and encouraging physical activity should be encouraged. Early recognition is also a key component of managing peripheral edema. Early and vigilant monitoring, such as measuring body weight and limb circumference, as well as close monitoring of the skin for swelling or erosions, is recommended to reduce the potential complexities related to this peripheral edema.

When a patient develops peripheral edema from MET TKIs, they need prompt intervention. Short treatment breaks appear to be the best option for management of this edema. Other conservative measures include compression stockings, lymphatic massage, and some massage therapists have specialties in this, limb elevation, exercise, and patients should be encouraged to continue with usual daily activities when they start on these therapies, but increased movement or even specialized exercises when they have onsets of edema.

We should encourage dietary changes, such as reduced salt and a balanced diet. And a diuretic can be considered as a potential option if patients have interference with their quality of life from the peripheral edema.

In the last section, we will review the other four toxicities from MET TKIs, and then finish with some practical considerations for using MET TKIs.

We will now discuss the incidence, monitoring, and management of the other four toxicities from this slide. The first toxicity we will evaluate is GI-adverse effects. The incidence of GI toxicities is fairly common in low grades, but thankfully the incidence in higher grades is quite low. This is one of the early toxicities patients experience, but it tends to resolve with continued treatment.

In terms of monitoring, the monitoring for these GI toxicities will be similar for what we typically do for any GI toxicities, such as ensuring adequate hydration if there is significant diarrhea and/or vomiting. Tepotinib should be taken with food, and capmatinib may be taken with or without food. But if a patient experiences GI toxicity, they could try taking capmatinib with food. GI disturbances don't often require MET TKI dose reductions or interruptions. However, this could be considered for patients who have grade 3 or higher toxicity.

The next toxicity we will look at is an increase in creatinine from MET TKIs. So, creatinine increases with MET TKIs are common, but mostly mild or moderate, and reversible. The incidence of severe creatinine increases is very low. Raised creatinine is typically associated with renal impairment, however, MET TKIs are known to inhibit creatinine transporters, causing creatinine levels to rise by approximately 25%.

Creatinine usually increases during the first few weeks of treatment and then levels off before returning to baseline after discontinuation of the medication. Non-clinically-relevant increases and plateau in creatinine levels might be expected with MET inhibitor use.

It is really important as oncology professionals that we have close monitoring of renal function, especially in the early months of treatment, to decide whether dose reductions or interruptions are needed. We should also consider other methods than creatinine-driven GFR to assess renal

function and to guide therapy. For grade 3 events, we need to evaluate whether somebody needs a treatment interruption or a dose reduction.

The next toxicity we'll look at is transaminase increases. Increased ALT, AST have been reported in patients with MET TKIs. Monitoring for liver function parameters is really important. However, most events, as you can see, are low grade and these events are reversible upon discontinuation of the agent.

It is also really important that we follow liver function tests really closely. So, we need to monitor liver function tests at baseline, every two weeks during the first three months of treatment, then once a month or as clinically indicated. We need to monitor these liver functions closer if the transaminases or bilirubin are elevated.

Dose interruptions are not usually required for grade 1 to 2 toxicities, unless the patient is symptomatic. And like the other toxicities, if it's a grade 3 or higher, we should be evaluating the patient for a dose interruption or a reduction.

The last toxicity we'll look at is interstitial lung disease. Interstitial lung disease is rare with these agents, but it has been reported, as you can see from the slide. The onset tends to occur quickly, usually within the first three months, but late presentations can occur even up to two years, so it's really important that we follow these patients closely for these toxicities.

Because ILD is potentially life-threatening, patients should be monitored during treatment for any signs of pulmonary issues. The product monographs for tepotinib and capmatinib are quite clear that they need immediate discontinuation of the drug when the patients have symptoms of ILD. It is also important to rule out other potential causes of ILD, if possible, and a referral to a pulmonary specialist should be made in cases where drug-induced ILD is suspected.

In this last slide, we will look at the practical aspects of using MET TKI inhibitors. As you can see from the half-life, tepotinib has a half-life of 32 hours, and capmatinib is much shorter at 6.5 hours. This could be beneficial with a shorter half-life if you need to withdraw the therapy because of toxicity.

Tepotinib is taken with food, and capmatinib may be taken with or without food. But as we discussed, if a patient is having GI toxicity, it may be better to take it with food. Tepotinib is dosed at once daily, and capmatinib is dosed at twice daily.

In terms of drug-drug interactions, if we look at the impact of the other drugs that the patient is taking on the MET TKIs, we can see that tepotinib is a substrate of 3A4 and transport proteins, but it's only minor. Capmatinib is a substrate of 3A4, but that's major, and a minor transport protein. We need to be careful when we use capmatinib with strong inducers or inhibitors of 3A4. In terms of the impact of the MET TKIs on the other drugs the patients are taking, we could see that both of these drugs inhibit transport proteins, and capmatinib also inhibits CYP1A2.

Finally, tepotinib does not have any drug-drug interactions with proton pump inhibitors, but capmatinib, when combined with a proton pump inhibitor, actually has a decreased AUC of 25%.

In summary, MET TKIs are generally well tolerated, most of the toxicities are mild to moderate, and hopefully manageable with supportive care and/or dose modifications. It is really important, though, as oncology clinicians, that we monitor our patients really closely for treatment related toxicities. Prevention, early recognition, and prompt intervention are critical to make sure that we have successful management of these toxicities to MET TKIs.

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