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Multidisciplinary Management of a Patient With Invasive Aspergillosis

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Announcer:
Welcome to ReachMD. This Medical Industry Feature, titled, “Multidisciplinary Management of a Patient With Invasive Aspergillosis” is sponsored by Astellas Pharma US, Inc. This program is intended for health care professionals.

Here’s your host, Dr Hana Safah.

Dr Safah:
Patients with invasive fungal infection often come with the complexities of their underlying disease and the resulting polypharmacy, typically consisting of long courses of antifungal therapy on top of their existing treatments. Effective management usually requires input and communication from multiple specialties through each aspect of the patient’s health care journey.

This is ReachMD, and I’m Dr Hana Safah. I am an hematologist-oncologist specializing in the treatment and research of blood cancers at Tulane Cancer Center.

Joining me to discuss the importance of a multidisciplinary approach in the management of invasive aspergillosis is our own multidisciplinary panel. Welcome, Dr Arthur Jeng, an infectious diseases specialist who works at Olive View UCLA Medical Center.

And Dr Lucas Schulz, a pharmacist and clinical coordinator of infectious diseases at the University of Wisconsin. Thank you for joining us.

We are also joined by Ms Nancy Skinner, a nurse case manager and educator at Riverside HealthCare Consulting in Whitwell, Tennessee. Thank you for being here.

Before we begin, let’s take a moment to review the Indications and Usage and some Important Safety Information for CRESEMBA. We will share portions of the Important Safety Information for CRESEMBA throughout the program.

Dr Schulz:
CRESEMBA (isavuconazonium sulfate) is an azole antifungal indicated for patients 18 years of age and older for the treatment of invasive aspergillosis and invasive mucormycosis.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) to isolate and identify causative organism(s) should be obtained prior to initiating antifungal therapy. Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

CRESEMBA is contraindicated in persons with known hypersensitivity to isavuconazole.

Coadministration of strong CYP3A4 inhibitors, such as ketoconazole or high-dose ritonavir, meaning 400 mg every 12 hours, with CRESEMBA is contraindicated because strong CYP3A4 inhibitors can significantly increase the plasma concentration of isavuconazole.

Coadministration of strong CYP3A4 inducers, such as rifampin, carbamazepine, St. John’s wort, or long acting barbiturates with CRESEMBA is contraindicated because strong CYP3A4 inducers can significantly decrease the plasma concentration of isavuconazole.

Finally, CRESEMBA shortened the QTc interval in a concentration-related manner. CRESEMBA is contraindicated in patients with

familial short QT syndrome.

Dr Safah:
All right, let's start by meeting our hypothetical patient. This is Lawrence. He's a 64-year-old male with acute myeloid leukemia, or AML. He had myelodysplastic syndrome, or MDS, for 18 months prior to his AML diagnosis. He also has a history of hypertension, type 2 diabetes, and moderate renal impairment. Lawrence, he's currently taking insulin and antihypertensives. He also has been taking hypomethylating agents for 14 months.

While in the hospital for induction chemotherapy, Lawrence develops a fever. He also notes black eschar at the top of a wound on his right lower extremity and assumes it is a wound that is not healing. He is prescribed antibiotics, but his fever does not resolve after a 5-day course.

So, after 5 days, Lawrence develops shortness of breath and continues to have persistent fever. He still has the black eschar on his right lower extremity, and his labs now show pancytopenia, renal impairment, and elevated liver function tests. His chest x-ray and CT scan of the chest are unremarkable. His blood and urine cultures are negative, and his beta-D-glucan is negative but he has elevated serum galactomannan. A fungal infection is thought to be likely, due to his history of prolonged neutropenia with MDS, along with his clinical presentation. His chest x-ray and CT scan of the chest did not suggest pulmonary aspergillosis, so a skin biopsy of the eschar is ordered, which comes back positive for *Aspergillus fumigatus*.

This is a complex patient who is diagnosed with a fungal infection on top of AML. My question to each one of you is, what would your role be in his initial management? Dr Jeng, why don't we start with you? When would you be called in to see a patient like this?

Dr Jeng:
Usually our hematology-oncology, or hem-onc, colleagues start the initial antibiotics. Since he remains neutropenic and febrile at Day 5, we would be called for further workup and help with the diagnosis.

Oftentimes, we will start with scans. A good physical exam here would show the eschar. In our experience, the beta-D-glucan seems to be more sensitive than the galactomannan for diagnosing fungal infections. If you do find something in the skin that's unusual, a biopsy is indicated.

So usually, we assist with the workup at this point in time as well as with the selection of the antifungal agent.

Dr Safah:
Thank you, Dr Jeng. Dr Schulz, what is your role with a patient like this? How early are you involved, and what are you asked to do?

Dr Schulz:
So, in this scenario, pharmacists are monitoring the effectiveness of antibiotics and indicating that it may be time to start an antifungal agent.

When we're starting an antifungal agent we're thinking about the most appropriate agent to start with. We base our decision on drug-drug interactions, adverse drug reactions, and pharmacokinetics. The disease state itself could play a role as alterations in renal or hepatic function might change drug pharmacokinetics.

We are also looking at how to administer the drug—IV versus oral—and how to ensure that the patient is getting the right amount of drug, and whether serum drug concentration monitoring is needed. We verify insurance to confirm that the drug will be accessible to the patient after discharge as well.

Dr Safah:
It's very helpful, Dr Schulz. Now I'll turn it over to Ms Skinner. How soon would you see a patient like this in the hospital? And when do you know they are ready to be discharged?

Ms Skinner:
Case managers in acute care facilities round with the whole multidisciplinary team. From the moment of admission, we're going to be working with each member of the team to develop a transitional care plan, not only looking at the components of the treatment plan, but also looking at the social determinants of health—such as where is the patient going after discharge or whether or not the home environment is appropriate. We communicate with the patient's health plan—all of the things that are part of making sure that the patient has a safe and appropriate health care journey.

Dr Safah:
Excellent, thank you for those insights. I have a follow-up question for everyone: What are some considerations you keep in mind when choosing an antifungal agent for a patient like Lawrence? Dr Jeng, let's turn back to you.

Dr Jeng:
Great question, Dr Safah. So, when choosing antifungals, we look at which agent is recommended and efficacious, if there are drug-drug interactions with the patient's current medications, or if there are any potential toxicities. For example, if a patient has renal or liver dysfunction, we'd look at whether or not they've had a prior reaction to any antifungal. These are all things we're taking into consideration when selecting the antifungal.

These days, we oftentimes select an azole agent and work with an infectious disease, or ID, pharmacist to determine the most appropriate azole.

Dr Safah:
It's truly a decision that's made by the team. Typically, I ask the team what's the goal of treatment and what the expectations of treatment are. For example, if liver enzymes are abnormal now, what would be the best treatment to maintain adequate liver function so I can take the patient to transplant and not worry about complications? And then we talk about how to manage the treatments. If a patient comes from far away for a follow-up, we need to determine, as a team, how to manage that.

I'd like to turn back to our patient Lawrence and discuss the specifics of his treatment. But before we do that, let's go over Warnings and Precautions from the Important Safety Information of CRESEMBA.

Dr Schulz:
Hepatic Adverse Drug Reactions (for example, elevations in ALT, AST, alkaline phosphatase, total bilirubin) have been reported in clinical trials and were generally reversible and did not require discontinuation of CRESEMBA. Cases of severe hepatic adverse drug reactions including hepatitis, cholestasis or hepatic failure including death have been reported in patients with serious underlying medical conditions (for example, hematologic malignancy) during treatment with azole antifungal agents, including CRESEMBA. Evaluate liver tests at the start and during therapy. Monitor patients who develop liver abnormalities during CRESEMBA therapy for severe hepatic injury. Discontinue if clinical signs and symptoms consistent with liver disease develop that may be attributable to CRESEMBA.

Infusion-Related Reactions including hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia were reported during intravenous administration of CRESEMBA. Discontinue the infusion if these reactions occur.

Hypersensitivity Reactions: Anaphylactic reactions, with fatal outcome, have been reported during treatment with CRESEMBA. Serious skin reactions, such as Stevens Johnson syndrome, have been reported during treatment with other azole antifungal agents. Discontinue CRESEMBA if anaphylactic or serious skin reactions occur, and initiate supportive treatment as needed.

It's also important to mention **Embryo-Fetal Toxicity:** During pregnancy, CRESEMBA may cause fetal harm when administered, and CRESEMBA should only be used if the potential benefit to the patient outweighs the risk to the fetus. Women who become pregnant while receiving CRESEMBA are encouraged to contact their physician.

Drug Interactions: Coadministration of CRESEMBA with strong CYP3A4 inhibitors such as ketoconazole or high-dose ritonavir, and strong CYP3A4 inducers such as rifampin, carbamazepine, St. John's wort, or long acting barbiturates is contraindicated.

Drug Particulates: Following dilution, CRESEMBA intravenous formulation may form precipitate from the insoluble isavuconazole. Administer CRESEMBA through an in-line filter.

Dr Safah:
We spoke a bit earlier about the initial management of Lawrence who was diagnosed with invasive aspergillosis during induction chemotherapy for AML. Now let's discuss his treatment with CRESEMBA as well as the pivotal trial data that led to the FDA approval of CRESEMBA.

Lawrence has started on CRESEMBA with a loading dose of 372 mg IV every 8 hours for 6 doses. Then he's transitioned to 372 mg of oral CRESEMBA, which is administered as two 186-mg capsules once daily, with an anticipated duration of therapy for 6 weeks.

Now we will discuss the Phase 3, randomized, double-blind, noninferiority trial for CRESEMBA, which evaluated its safety and efficacy versus voriconazole for primary treatment of invasive fungal disease caused by *Aspergillus* species or other filamentous fungi.

Eligible patients included men and women age 18 years or older, with proven, probable, or possible invasive fungal infections based on the European Organisation for Research and Treatment of Cancer Mycoses Study Group criteria. The majority of patients were male, Caucasian, and had fungal disease involving the lungs. The intent-to-treat population included all randomized patients who received at least one dose of study drug. Patients with moderate to severe renal impairment were excluded due to labeling restrictions associated with the active comparator.

Patients were treated with CRESEMBA by intravenous, or IV, administration at the loading dose of 372 mg isavuconazonium sulfate every 8 hours for the first 48 hours, and a maintenance dose of 372 mg isavuconazonium sulfate via IV or orally once daily from Day 3 onward. Patients treated with voriconazole received a loading dose of 6 mg/kg IV every 12 hours for the first 24 hours, followed by a maintenance dose of 4 mg/kg IV every 12 hours for 24 hours, then 4 mg/kg IV every 12 hours or were switched to 200 mg PO every 12 hours.

It is important to note that with regard to risk factors for invasive fungal disease, most patients in the study had a hematologic malignancy at baseline.

As expected, neutropenia was also highly prevalent.

The primary endpoint of all-cause mortality through Day 42 in the intent-to-treat population was 18.6% in the CRESEMBA treatment group and 20.2% in the voriconazole treatment group.

Similar results were seen in the population with proven or probable invasive aspergillosis confirmed by serology, culture, or histology: 18.7% with CRESEMBA and 22.2% with voriconazole.

The mean treatment duration was 47 days for both treatment groups, of which 8 to 9 days were by IV route of administration.

Let's review some additional Important Safety Information.

Dr Schulz:
The most frequently reported adverse reactions among CRESEMBA-treated patients were: nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), elevated liver chemistry tests (16%), hypokalemia (14%), constipation (13%), dyspnea (12%), cough (12%), peripheral edema (11%), and back pain (10%).

The adverse reactions which most often led to permanent discontinuation of CRESEMBA therapy during the clinical trials were: confusional state (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnea (0.5%), epilepsy (0.5%), respiratory failure (0.5%), and vomiting (0.5%).

Dr Safah:
Dr Schulz, would you like to present a little bit about the pharmacology of CRESEMBA?

Dr Schulz:
I'd be happy to. CRESEMBA is the prodrug of isavuconazole, an azole antifungal drug. There was no significant association between area under the curve or drug concentration and efficacy in patients treated for invasive aspergillosis in a controlled trial. Dose-proportional pharmacokinetics were observed following oral administration of CRESEMBA capsules at doses up to the equivalent of 600 mg/day of isavuconazole, or 6 capsules. CRESEMBA demonstrates 98% absolute bioavailability following oral administration and reaches maximum plasma concentration in 2 to 3 hours. It is extensively distributed throughout the body. CRESEMBA results in a dose-related shortening of the corrected QT interval.

Dr Safah:
Thank you, Dr Schulz. So my next question is, why we, as a multidisciplinary team, would choose to start a patient like Lawrence on CRESEMBA? We can go back to the indication and see that CRESEMBA is indicated in his case.

Dr Jeng, why might CRESEMBA be a good choice for Lawrence?

Dr Jeng:
It would be a good option for Lawrence because he has mild liver abnormalities and some issues with renal function. We will follow his liver enzymes closely throughout therapy, but there is no need to adjust the CRESEMBA dose.

I also think about the potential for drug-drug interactions, and I'm comfortable managing those potential interactions with CRESEMBA.

Dr Safah:
Thank you, Dr Jeng. Dr Schulz, from a pharmacist's perspective, what are you looking for when you select treatment?

Dr Schulz:
Well, I would ask, what does the patient's AML look like? How long do we expect them to remain neutropenic? That gives me an idea of how long the treatment duration may last. And CRESEMBA has shown tolerability in a 6-month timeframe.

And then I would think of access. What is the patient's coverage for outpatient care, and are they able to seamlessly transition from inpatient to outpatient care?

Dr Safah:
Ms Skinner, given your expertise in transitions of care, what are your thoughts on this?

Ms Skinner:
I believe the key is that CRESEMBA is an oral medication that can be administered once daily. This patient might be on other medications when he goes home from the hospital. So adherence might be easier to achieve for this patient with a once-daily medication. I would also want to be sure that he has insurance coverage. As a nurse case manager, I'm focusing on the continuity of care with regard to his medical condition and some social determinants of health. A social worker might also be involved in this patient's health care journey.

Dr Safah:
Thank you for those excellent points, Ms Skinner. Now let's move on to discuss our patient Lawrence. As a hematologist-oncologist, I'm going to monitor him in the hospital with physical exams, neutrophil counts, complete blood count, liver enzymes, kidney function, and galactomannan level.

What would you be looking for, Dr Jeng?

Dr Jeng:
Of course we look at the vitals, to make sure the fever goes away on the antifungal. That could tell us that yes, the fungus was the culprit for the fevers, and not bacteria per se.

We also want to make sure that the fungus isn't spreading to other parts of the body. With *Aspergillus*, we know that it can go to other parts of the body besides the sinuses and the lungs, which can include the brain.

So we'll be asking about headaches and vision changes. And then from the lab standpoint, we'll also be following along with our hem-onc colleagues.

Dr Safah:
Thank you, Dr Jeng. Dr Schulz, how is the ID pharmacist involved in the monitoring of such a patient?

Dr Schulz:
CRESEMBA is a medication that filters through a very common drug-drug interaction pathway, the CYP3A4 pathway, so pharmacists should be able to identify potential drug-drug interactions. We would need to assess for drug interactions any time a medication is added or stopped.

With CRESEMBA, we typically do not have to monitor serum drug levels, which simplifies things a bit.

We also monitor for compliance to make sure that the patient's taking their medications, that they're filling prescriptions at expected time intervals, and that they aren't frequently missing doses.

Dr Safah:
Excellent points, Dr Schulz. Ms Skinner, how would you be involved in supporting our patient at this stage?

Ms Skinner:
There has to be an established continuum of care plan that includes input from each member of the multidisciplinary team. Is there going to be any monitoring post discharge? Does the patient know what symptoms to look for? Who's providing patient education? Has a pharmacist talked to the patient while they're in the hospital?

There should be patient understanding of what the medication is doing at discharge, the value of taking it, and conversely, what may happen if the patient doesn't take the medication.

If they're going home, is the home environment able to support them and minimize their risk for any complications? Is there someone to support the patient? Have we reached out to the community continuing care team, for example, the primary care provider or the endocrinologist who's managing the patient's diabetes? We want all members of the team working collaboratively to help the patient achieve the goals that they want to achieve.

Dr Safah:
Thank you, Ms Skinner. Finally, I would like to ask each of you how would you be involved in Lawrence's transition of care from the hospital to home and what that might look like.

As a hematologist-oncologist, one of my goals would be to see Lawrence through to transplant, so I would examine him frequently to be sure he is progressing as expected. So I am following the patient on a regular basis with my ID colleagues. We usually alternate with respect to the outpatient follow-up.

Dr Jeng, how might a care transition work at your center?

Dr Jeng:
Generally, we'll follow up in about a month's time in our clinic. We have an extensive electronic medical records, or EMR, communication system amongst all the hem-onc and ID colleagues, so if there's a question about discontinuing medication, we can easily communicate with our hemo-onc colleagues via our EMR system.

Dr Safah:
Dr Schulz, does the inpatient pharmacist ever follow up on a patient like this once the patient leaves the hospital?

Dr Schulz:
At our institution, we have a handoff procedure. Our inpatient pharmacist writes a note that goes to the hem-onc clinic saying that our patient Lawrence was seen and was started on CRESEMBA for invasive aspergillosis. The note will include what to monitor for and is essentially an FYI about any changes that happened on the inpatient side that need to be communicated to the outpatient pharmacist.

Dr Safah:
That's a great practice. Ms Skinner, I'll turn it over to you. How will the case manager follow up with this patient at home?

Ms Skinner:
Many facilities have a process where there's a transitional care management team that'll reach out to the patient following discharge to be sure that they have obtained their medications.

In most cases, we call the patient to see how they are doing and ask, do you know what you need to do? Are there any barriers to achieving your goals? What other medications are you taking?

We're really trying to get an idea of what's going on in the home environment. If any red flags arise, we certainly will reach out to the physician to see if we need to have some sort of supportive care, or evaluation by home health care to see how that patient is truly doing in the home environment.

Dr Safah:
Thank you, Ms Skinner. The process you describe truly places the patient's needs and concerns at the center of their care transition. I think we can all appreciate this approach.

Now let's follow up with our patient Lawrence one last time before we close our discussion. Once his fever resolved and the white blood cells recovered, Lawrence was discharged home on CRESEMBA. He was monitored in the outpatient clinic every week for the first 4 weeks, then every 2 weeks thereafter until his infection resolved and the site of the eschar was negative for ongoing fungal infection. And he later underwent stem cell transplant.

That brings us to the end of today's program. I want to thank my guests for helping us better understand the importance of a multidisciplinary approach to the management of invasive aspergillosis. Dr Jeng, Dr Schulz, Ms Skinner, it was great speaking with you all today.

Announcer:
This promotional program was developed and sponsored by Astellas Pharma US, Inc. Dr Safah, Dr Jeng, Dr Schulz, and Ms Skinner received a fee for participation in this program.

References:
Astellas. CRESEMBA. Data on File.
Cresemba [package insert]. Northbrook, IL: Astellas Pharma US, Inc.
Desai AV, Kovanda LL, Hope WW, et al. Exposure-response relationships for isavuconazole in patients with invasive aspergillosis and other filamentous fungi. Antimicrob Agents Chemother 2017;61(12):e01034-17.
DiPippo AJ, Kontoyiannis DP. Lack of toxicity with long-term isavuconazole use in patients with hematologic malignancy. Clin Infect Dis 2019;69(9):1624-7.
Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet 2016;387(10020): 760-9.

Thompson GR III, Patterson TF. *Aspergillus* species. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Philadelphia, PA: Elsevier Saunders, 2020:3103-16.

Announcer: