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Managing Capillary Leak Syndrome: Early Recognition and Intervention in BPDCN Care

ReachMD Announcer:
Welcome to *Project Oncology* on ReachMD. This medical industry feature, titled “Managing Capillary Leak Syndrome Associated with Tagraxofusp: Early Recognition and Intervention in BPDCN Care,” is developed by Stemline Therapeutics, Inc. US Medical Affairs. This activity is intended for United States healthcare professionals only.

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And now, here’s your host, Dr. Jennifer Caudle.

Dr. Caudle:
Blastic plasmacytoid dendritic cell neoplasm, or BPDCN for short, is a rare and aggressive hematologic malignancy that, historically, has had poor clinical outcomes.[1] But the landscape changed in 2018, as the FDA approved tagraxofusp, a CD123-directed therapy and the first treatment specifically indicated for BPDCN in adults and pediatric patients two years and older.[2]

This is *Project Oncology* on ReachMD, and I’m your host, Dr. Jennifer Caudle. And today, we’ll explore how clinicians treating BPDCN with tagraxofusp can recognize and manage capillary leak syndrome, or CLS, using a stepwise clinical approach.

Joining me today is Dr. James McCloskey who’s the Chief of the Division of Leukemia at Hackensack Meridian John Theurer Cancer Center, part of the Hackensack University Medical Center.

Dr. McCloskey, thank you so much for being here.

Dr. McCloskey:
Thanks for having me. It's a pleasure.

Dr. Caudle:
And, before we jump into our discussion, let’s review highlights of the prescribing information, including indication and BOXED WARNING, for tagraxofusp.

ReachMD Announcer:
Highlights of Prescribing Information

INDICATION

Tagraxofusp is a CD123-directed cytotoxin indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older.

BOXED WARNING: CAPILLARY LEAK SYNDROME

Capillary Leak Syndrome (CLS) which may be life-threatening or fatal, can occur in patients receiving tagraxofusp. Monitor for signs and symptoms of CLS and take actions as recommended.

Please stay tuned to the whole program to hear highlights of the prescribing information for tagraxofusp.

Dr. Caudle:
Now that we've heard the product indication and BOXED WARNING, Dr. McCloskey, let's begin with the basics. What exactly is CLS?

Dr. McCloskey:
CLS is a condition of vascular permeability that can result from different diseases such as autoimmune disorders and, importantly, cancer. It's also associated with several other anticancer treatments, including gemcitabine IL-2 and checkpoint inhibitors, so CLS isn't unique to just tagraxofusp.[3]

Clinically, with CLS we'll see hypoalbuminemia, edema, weight gain, and hypotension in the prodromal phase.[4,5] This is because plasma and protein-rich fluid is leaking from the intravascular space into the interstitial tissues.[6]

Then in the post-leak phase, there's an increased risk of fluid overload once leakage from the capillaries abates and protein-rich fluids are reabsorbed from the tissues. Here, we may see pulmonary edema, cardiopulmonary failure, and deep vein thrombosis.[5]

And so recognizing signs and symptoms of CLS early is critical to reduce the risk of severe sequelae, which can include multi-organ failure and death.[6-8]

Although the exact mechanisms aren't completely understood, CLS caused by anticancer agents may result from an excessive production of cytokines.[3,5,9]

But before we dive further into CLS, it's important that we distinguish this process from *CRS*, or cytokine release syndrome. CRS is an acute inflammatory response with symptoms that include fever and hypoxia, while *CLS* has different manifestations of vascular hyperpermeability leading to hypoalbuminemia and edema.[10]

The management strategies for each is also different. CLS is typically managed with albumin, fluid management, and corticosteroids, while CRS treatments may include alternative agents such as IL-6 blockade.[10]

That's why again, early identification of both CLS and CRS is important to provide appropriate intervention.[10]

Dr. Caudle:
Thanks for that background, Dr. McCloskey. And if we now turn to tagraxofusp, or TAG, could you tell us about how it works in BPDCN treatment?

Dr. McCloskey:
Certainly. TAG targets the surface protein CD123, which is expressed by malignant cells. It's a fusion protein that combines IL-3 with a truncated diphtheria toxin. The IL-3 component binds to CD123-positive cells, delivering the diphtheria toxin into them, where it inhibits protein synthesis and induces apoptosis.[1,2,11]

Interestingly, CD123 is *also* expressed on vascular endothelial cells, which may help explain why TAG has a risk of CLS. The working theory is that endothelial uptake of the drug leads to cell death and vascular leakage.[5,9]

Dr. Caudle:
So then let's talk about the data. How did TAG perform in clinical trials for BPDCN?

Dr. McCloskey:
Well, TAG was approved based on the pivotal study STML-401-0114, which was an open-label, single-arm, multicenter, Phase One/Two study.[2,12] In the pivotal cohort of 13 treatment-naïve patients, 53.8 percent achieved a complete or clinical complete response, or CR/CRc for short. The median duration of CR/CRc wasn't reached at the median follow-up of 11.5 months.[2]

In total, the study enrolled 65 front-line patients and 19 relapsed.[1]

In all evaluable front-line patients with a median duration of follow-up of 34 months, the overall response rate was 75 percent and the CR/CRc rate was 57 percent. The median time to CR/CRc was 39 days and the median *duration* of CR/CRc was 24.9 months.[1,13]

A key point is that just over half of those responders—51 percent—were able to proceed to stem cell transplant, which is often the curative goal in BPDCN. These patients had a median overall survival of 38.4 months, with a confidence interval of 3.4 to 58.1 months.[1,13]

And that's why managing safety—especially early toxicities like CLS—is essential to help patients stay on therapy long enough to derive the optimal benefit of the treatment.[1]

Dr. Caudle:
And as a follow-up, what did the safety profile look like for TAG?

Dr. McCloskey:
The safety population of the -0114 study encompassed all patients receiving TAG, which patients with relapsed refractory acute myeloid leukemia, or AML. Outside of capillary leak, the most frequent adverse events seen in at least 30 percent of patients included nausea, fatigue, pyrexia, peripheral edema, and weight gain.

The most common laboratory abnormalities occurring in at least 50 percent of patients were decreases in albumin, platelets, hemoglobin, calcium, and sodium, and increases in glucose, ALT, and AST.[1,2,13]

So overall, TAG demonstrated a well-characterized safety profile. Transient adverse events mostly occurred in Cycle One, and there was no cumulative hematologic or non-hematologic toxicities. Of note, at the 2024 American Society of Hematology Annual Meeting, TAG demonstrated stabilization of hematologic parameters from the end of Cycle One. This included reduction of platelet and RBC transfusions – indicating restoration of normal hematopoiesis.[1,2,13,14]

Now, if we look at the CLS rates in the -0114 study, investigator-led clinical assessment identified CLS in 18 patients, or 21 percent, of both treatment-naïve and relapsed/refractory BPDCN patients. The majority of cases were Grade Two. The median time to onset of CLS was six days, with only one event occurring outside of Cycle One. And the median time to CLS resolution was six days overall and nine days in patients with a Grade Three or higher events.[1]

Among all 122 patients receiving 12 micrograms per kilogram of TAG in the study—which included patients with relapsed acute myeloid leukemia—four patients, or three percent, had fatal adverse reactions, all of which were related to CLS.[2]

It's important to note that most of these events were transient, and there wasn't evidence of cumulative toxicity with ongoing treatment, as most of the events occurred in Cycle One.[1]

Dr. Caudle:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jennifer Caudle, and today I'm speaking with Dr. James McCloskey about CLS recognition and management in patients with BPDCN treated with tagraxofusp.

Now, I understand that there's a difference in the CLS rates reported in the study manuscript compared to what's reported in the prescribing information for TAG. Dr. McCloskey, can you walk us through that?

Dr. McCloskey:
Absolutely. What's important to know is that there are two ways that CLS has been determined in this study: by investigator assessment and by FDA algorithm.

When investigators in the pivotal study identified CLS based on investigator assessment, the reported incidence was 21 percent, as I mentioned earlier.[1] But in the US Prescribing Information for TAG, the CLS rate based on the FDA algorithm was closer to 53 percent. The FDA algorithm defines CLS in patients if they have at least two of the following within a seven-day window[2]:

- hypoalbuminemia,
- edema—including a weight increase over five kilograms,
- or hypotension.

As a result of applying these criteria, additional cases of CLS were identified, with the majority of these cases being Grade One or Two.[2]

Dr. Caudle:
That's interesting. And let's review some real-world data now. The Named Patient Program is a cohort of about 40 patients treated for BPDCN in either first-line or relapsed/refractory settings that was evaluated in a non-interventional, retrospective, observational, multicenter, single-arm study.[15] So what were the results of the findings?

Dr. McCloskey:
Well, what we saw in this retrospective real-world study was that there were no Grade Five CLS events and only one Grade Four event reported. CLS events were similar to those reported with the FDA algorithm, with 45 percent of treatment-naïve and 61 percent of relapsed/refractory patients having CLS. All of these cases resolved, and there were no CLS-related deaths.[16,17]

What's notable about this program was that all participating sites had to complete safety training before initiating TAG. So these findings really underscore how preparation and team readiness is an important first step in optimizing patient outcomes.[15-17]

Dr. Caudle:
And to apply this knowledge in practice, PLAN is an algorithm for administering TAG and managing potential adverse events. Can you take us through the PLAN management guide?

Dr. McCloskey:
I'd be happy to. PLAN is a proactive, structured approach to identify and manage CLS with TAG. I'll walk through each step of PLAN, starting with P, which is to *prepare* for treatment initiation.

Here, we aim to ensure we have an appropriate patient to start TAG. So we're looking for a serum albumin of at least 3.2 grams per deciliter.[2] We're also assessing cardiac function with both an electrocardiogram and an echocardiogram to ensure the left ventricular ejection fraction is greater than the institutional lower limit of normal.[11]

Beyond the initial patient assessment, preparation also means having the right infrastructure in place. We'll confirm all dosing and administration supplies are available, including a syringe pump.

And for Cycle One, we *always* administer TAG as an inpatient with close observation for at least 24 hours after the last dose. As a reminder, the dosing of TAG is 12 micrograms per kilogram on days one through five of a 21 day cycle. The dosing period may be extended for dose delays up to day 10 of the cycle. After Cycle One, administration can take place in an outpatient facility, with continued laboratory, physical exam, and post-infusion monitoring.[2]

The next stage is L, which is to *look* for signs and symptoms of adverse events.

For CLS, we can use the acronym WELL for signs to monitor daily: weight gain, edema, low albumin, and low blood pressure. These markers can give us an early signal that CLS may be developing.[2]

And at certain thresholds, we need to hold TAG;[2] these include:

- A weight gain of 1.5 kilograms or more from the previous day's weight,
- A drop in albumin by at least 0.5 grams per deciliter from their baseline albumin or any albumin value less than 3.5 grams per deciliter,
- Or systolic blood pressure at or below 80 millimeters of mercury.

We're also monitoring AST, ALT, serum creatinine, changes in vital signs, as well as for hypersensitivity reactions. [2]

Keep in mind that patients are premedicated 60 minutes before each infusion with histamine antagonists, corticosteroids, and acetaminophen to help with hypersensitivity reactions.[2,18]

Then we'll move into A, which is to *apply* management and supportive care. If there's concern for CLS, this is the moment to intervene. In addition to holding TAG, we'll initiate supportive care based on the patient's presentation, which may include the following interventions[2]:

- Intravenous albumin at 25 grams every 12 hours, or more frequently if practical,
- Fluid management, such as IV fluids and possibly vasopressors for hypotension, or diuretics if the patient's fluid-overloaded,
- And corticosteroids, typically methylprednisolone at one milligram per kilogram per day

And finally, we get to N, which is deciding on *next* steps for TAG treatment.

TAG can only resume in the same cycle if CLS signs and symptoms resolve within the 10-day dosing window *and* no IV fluids or vasopressors were used for the treatment of hypotension. Otherwise, we'll need to hold treatment and wait until the next cycle.[2]

Dr. Caudle:
Thanks for walking us through that, Dr. McCloskey. And before we wrap up, what practical strategies could help improve the success of PLAN?

Dr. McCloskey:
A few tactical steps can make PLAN implementation most effective[15-17]:

- First, as we saw in the NPP study, we want to train the whole care team before we start treatment— this includes physicians, nurses, pharmacists, and advanced practice providers. Everyone needs to know what CLS looks like and what to do when signs and symptoms appear.
- Next, it's helpful to begin infusions early in the week with infusions occurring mid-day to ensure full staff coverage.
- Finally, before beginning treatment, it's important to make sure the pharmacy has albumin available.

The PLAN framework—Prepare, Look, Apply, and Next—provides a clear roadmap for recognizing and responding to CLS.

And multidisciplinary team training and readiness can help transform this framework from guidance into real-world success.[15-17]

Dr. Caudle:
Thanks for sharing those final thoughts with us, Dr. McCloskey. And now, let's hear highlights of the prescribing information for tagraxofusp.

ReachMD Announcer:
Warnings and Precautions

- **Capillary Leak Syndrome:** Before initiating therapy with tagraxofusp, ensure that the patient has adequate cardiac function and serum albumin is greater than or equal to 3.2 g/dL. During treatment with tagraxofusp, monitor serum albumin levels prior to the initiation of each dose of tagraxofusp and as indicated clinically thereafter, and assess patients for other signs or symptoms of CLS, including weight gain, new onset or worsening edema, including pulmonary edema, hypotension or hemodynamic instability.
- **Hypersensitivity:** Monitor patients for signs/symptoms and treat appropriately.
- **Hepatotoxicity:** Monitor ALT and AST. Interrupt tagraxofusp if the transaminases rise to greater than five times the upper limit of normal.

Adverse Reactions

- Most common adverse reactions (incidence ≥ 30%) are capillary leak syndrome, nausea, fatigue, pyrexia, peripheral edema, and weight increase. Most common laboratory abnormalities (incidence ≥ 50%) are decreases in albumin, platelets, hemoglobin, calcium, and sodium, and increases in glucose, ALT and AST.

Use in Specific Populations

- **Lactation:** Advise women not to breastfeed. Breast feeding is not recommended during treatment and for 1 week after the last dose.

Please see full Prescribing Information, including Boxed WARNING.

Dr. Caudle:
As that brings us to the end of our program, I'd like to thank my guest, Dr. McCloskey, for sharing his insights on managing CLS with tagraxofusp for BPDCN. Dr. McCloskey, it was great speaking with you today.

Dr. McCloskey:
Thanks. It was also great to be here. Thanks everyone for their time, and I hope this helps your patients.

ReachMD Announcer:

If you missed any part of this discussion or to find others in this series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge.

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