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# A Case Report Of Tragaxofusp Causing Severe Tumor Lysis Syndrome In A Patient With Blastic Plasmacytoid Dendritic Cell Neoplasm

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## INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematologic malignancy that does not respond to cytotoxic chemotherapies well. We present a case of BPDCN that was treated with a new targeted therapy tagraxofusp and the fatal complication that the patient developed with this treatment.

## HOSPITAL COURSE

The patient was an 83-year-old male without significant past medical history who presented to his primary care physician with several days of generalized malaise. He obtained routine bloodwork which showed a leukocytosis to 29 B/L. He then presented to the ED for further evaluation. Vitals were within normal limits and physical exam was remarkable for splenomegaly. Labs were significant for a WBC 44.7 B/L, Hgb 10 g/dL, platelets of 96 B/L, and the differential showed 20.6 B/L blasts. Creatinine was increased from a baseline of 1.20 to 1.45mg/dL, potassium was 4.9mmol/L, phosphate was 3.1mg/dL, calcium was 8.5 mg/dL, lactate dehydrogenase was 2705 IU/L, and uric acid was 5.1mg/dL. A peripheral smear was done which showed immature leukocytes with blastic morphology. He was admitted for further hematologic malignancy workup.

Flow cytometry of the peripheral blood showed a population that was CD4+, CD7+(dim), CD33+(dim), CD38+(partial, bright), CD56+(partial, bright), CD 123+, HLA-DR+(bright) and a monoclonal CD5+CD23+ B cell population. These markers show an undifferentiated blast population specific for neither lymphoid nor myeloid lineage. Fluorescence in-situ hybridization (FISH) showed 17p (TP53) deletion, 13q deletion (D13S319 and LAMP1), and ZRSR2 mutations. A complete karyotype revealed multiple complex chromosomal abnormalities with the presence of two unrelated abnormal clones suggesting genomic instability as well as the clonal evolution of neoplastic cells. Bone marrow biopsy showed hypercellularity and 84% immature-appearing cells. The abnormal cells had following phenotype: CD4+, CD10, CD13-, CD14-, CD16-, CD33+ (partial, dim), CD34-, CD38+, CD56+ (partial), CD64-, CD117- , HLA-DR+. These immature cells express CD123 and were

negative for MPO by peripheral blood flow cytometry. By immunohistochemistry, the neoplastic cells were positive for CD4, CD43, CD56 (dim, partial), and TCL-1 (diffuse and strong). Notably, they were negative for CD68, CD163, lysozyme, and MPO. These findings are consistent with the diagnosis of blastic plasmacytoid dendritic cell neoplasm (BDPCN). Additionally, flow cytometry detected a small monoclonal B-cell population (6%) with phenotype consistent with chronic lymphocytic leukemia/small lymphocytic lymphoma. Further assessment by computed tomography (CT) of the abdomen and pelvis revealed massive splenomegaly to 23cm but did not show evidence of metastatic disease or lymphadenopathy in the chest, abdomen, and pelvis.

The patient was subsequently started CD123 targeted therapy with tagraxofusp at a dose of 12 mcg/kg three days after admission. His lab values remained stable from admission to initiating therapy. On cycle 1, day 1, approximately 6 hours after he finished his first infusion, the patient was found to have altered mental status with increasing dyspnea and tachypnea to 50's with desaturation to 80% on room air. Labs obtained at the time showed a WBC 130.5 B/L, Hgb 9.5g/dL, platelets of 102 B/L, and the differential showed 117.5 B/L blasts. His creatinine was 2.11mg/dL, potassium 7.4mmol/L, phosphate 10.9mg/L, LDH 20119 IU/L, and urate of 5.8mg/dL. The patient was placed on non-invasive positive pressure ventilation and diuresis was given without significant improvement. The decision was made to intubate and he was transferred to the medical intensive care unit. The patient's acute hypoxic respiratory failure was thought to be due to a combination of capillary leak syndrome and tumor lysis syndrome resulting in anuric acute kidney injury and fluid retention.

After his arrival to the intensive care unit, the patient was febrile with temperature 102.4 F, hypotensive with BP 111/33, and bradycardic to 51 BPM. He was given more diuresis with IV furosemide 100mg and started on vancomycin and cefepime. Telemetry showed changes consistent with hyperkalemia including peaked T-waves and bradycardia. Temporizing measures were given including insulin, dextrose, and bicarbonate infusion. However, he ultimately required continuous veno-venous hemodialysis (CVVHD) due to the severity of his electrolyte derangements. During the patient's ICU

course, he developed seizure-like activity. CT of the head was negative for any acute changes such as edema or hemorrhage. An electroencephalogram (EEG) was done but was negative for seizure activity. The patient then developed shock liver with elevations in AST 2859, ALT 2205, ALP 108, and had a lactate of 11.9. He also had multiple episodes of supraventricular tachycardia with heart rates up to 170 BPM, which required adenosine and cardiac resynchronization therapy. Due to the severity of the patient's condition and the wishes of the patient's family, aggressive care was stopped and the patient's care was switched to comfort measures only. He passed away on cycle 1, day 4, after a palliative extubation.

## DISCUSSION

BPDCN is an aggressive hematologic malignancy. One of the characteristics of this malignancy is that the neoplastic cells almost always overexpress interleukin-3 receptor subunit alpha (IL3RA or CD123). Tagraxofusp, as a CD123-directed cytotoxin consisting of recombinant human interleukin-3 fused to a truncated diphtheria toxin, targets this overexpression specifically.<sup>1</sup> In 2019, a nonrandomized, multistage, open-label, multicenter evaluation of tagraxofusp as monotherapy in patients with BPDCN study was published in the NEJM and a 90% overall response rate was observed among patient with previously untreated BPDCN, and the majority of responses were complete remission. In contrast, prior to the development of tagraxofusp, there was no standard treatment for BPDCN. BPDCN was treated with cytotoxic chemotherapy regimens that were conventionally used for treating acute lymphoblastic leukemia/large B cell lymphoma, non-Hodgkin lymphoma, or acute myeloid leukemia but with very limited success. Although the standard-of-care remains untested in randomized fashion, tagraxofusp exhibits a higher rate of complete responses when used in the first-line setting. Because of this presumed efficacy and his advanced age putting him at higher risk for intensive induction chemotherapy, we chose tagraxofusp as our therapy of choice.

The most serious adverse events of tagraxofusp that has been reported is capillary leak syndrome.<sup>2</sup> Capillary leak syndrome is characterized by leakage of intravascular fluids into the extravascular space, leading to generalized edema, pulmonary edema and multiorgan failure. In the Pemmaraju et al study, 9 patients (19%) had capillary leak syndrome of various grade and two deaths that were attributed to capillary leak syndrome. Tumor lysis syndrome was also described as a less common and less severe adverse event of tagraxofusp in this study. In total, 11% of the patients had  $\geq$  grade 3 tumor lysis syndrome.<sup>2</sup> However, no deaths were reported to be associated with tumor lysis syndrome.

In our patient's case, he developed an overwhelming response to the tagraxofusp immediately after his first dose. His anuric acute kidney injury secondary to tumor lysis syndrome led to metabolic derangements, cardiac instability and death. As potential adverse effects are not fully known for this new agent, we suggest that this case should raise awareness of the potential severity of tumor lysis syndrome with tagraxofusp. In addition, cytoreduction could be considered prior to the start of tagraxofusp in patients with high tumor burden to decrease the risks of developing tumor lysis syndrome.

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