Treatment of Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) in Pediatric Patients With Tagraxofusp, a CD123-Targeted Therapy

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INTRODUCTION

- Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive orphan hematologic malignancy that has a poor prognosis[1,2]
  - It is derived from the precursors of plasmacytoid dendritic cells that overexpress CD123, the interleukin (IL)-3 receptor alpha
- BPDCN is primarily a disease of the elderly, although pediatric patients make up 10–20% of cases, and clinical presentation appears to be similar[2,3]
- Tagraxofusp (TAG) is a first-in-class, recombinant human IL-3 fused to a truncated diphtheria toxin payload that targets CD123[4], a molecule that is overexpressed in all cases of BPDCN
- TAG was approved by the US FDA for patients aged ≥2 years with newly diagnosed and relapsed or refractory (R/R) BPDCN in 2018[5] and as first-line (1L) treatment for adult patients by the EMA in 2021[6]
  - Approval was based on the safety and efficacy results of a pivotal study with TAG monotherapy (overall response rate 75%; complete response [CR] plus clinical CR [CRc] 57%; median duration of CR+CRc 24.9 months)[5–7,8]
- Although no pediatric patients were enrolled in the pivotal study, approval in the US for use in pediatric patients was granted based on the biologic similarity of BPDCN in adults and children
  - In addition, data from a case series of 3 pediatric patients with BPDCN has demonstrated that TAG led to rapid and significant clinical improvement with minimal toxicity in 2/3 patients[9]
- Herein, we present a case series of pediatric/young adult patients with BPDCN treated with TAG monotherapy, to provide further insight into the efficacy and safety of TAG treatment in this ultra-rare population

METHODS

- Multicenter retrospective collation of case reports of pediatric/young adult patients (≤21 years) diagnosed with BPDCN at 6 centers in the US and Europe
- All patients were treated according to local institutional guidelines and received TAG either as 1L treatment or for R/R disease
- Data were collected through chart review and summarized descriptively
- Safety was assessed via monitoring for adverse events (AEs) and laboratory abnormalities
- Efficacy was evaluated through tumor responses and survival

RESULTS

Patients

- Clinical data were collected from 8 pediatric/young adult patients with BPDCN who had received TAG during their course of treatment
- The median age was 15.5 years (range 2-21) and most patients were female (88%) (**Table 1**)
- All patients received TAG at 12 mcg/kg, while 1 patient also received TAG at a lower dose of 7 mcg/kg at time of second relapse
- The median number of TAG cycles received was 3.5 (range 1–4)
- Individual case details for each patient are presented in the **Figure** and **Table 2**

Figure. Patient Case Overview

Patient 1
- 21-year-old female
- 1L BPDCN
- Presented with an enlarging 3-cm lesion on left calf; no evidence of BM disease

Patient 2
- 20-year-old male
- 1L BPDCN
- Presented with raised skin lesions on scalp and upper back; no evidence of BM disease

Patient 3
- 16-year-old female
- 1L BPDCN
- Presented with bilateral posterior auricular and sub-mandibular adenopathy; right supraclavicular and bilateral axillary lymphadenopathy; BM, skin, and CNS involvement

Patient 4
- 16-year-old female
- 1L BPDCN
- Presented with a large 6-cm lesion on the right leg; no BM or CNS involvement

Patient 5
- 15-year-old female
- 1L BPDCN
- Presented with 70% BM infiltration; abdominal and inguinal LN involvement; no skin involvement

Patient 6
- 15-year-old female
- R/R BPDCN
- Presented with skin lesion on left breast; no BM or CNS involvement

Patient 7
- 10-year-old female
- R/R BPDCN
- Presented with skin lesion on left cheek; BM and LN involvement; no CNS involvement

Patient 8
- 2-year-old female
- R/R BPDCN
- Presented with fever and otitis media; BM involvement; no skin involvement

Table 1. Patient Characteristics and TAG Treatment

Characteristic	Patients N=8
Median age, years (range)	**15.5** (2-21)
Sex, n (%)	
Female	**7** (87.5)
Male	**1** (12.5)
Treatment, n (%)	
1L	**5** (62.5)
R/R	**3** (37.5)
Presentation, n (%)	
Skin lesions	**6** (75.0)
Bone marrow involvement	**5** (62.5)
Lymph node involvement	**3** (37.5)
TAG dose, n (%)	
12 mcg/kg	**8** (100.0)
7 mcg/kg[a]	**1** (12.5)
TAG cycles, median (range)	**3.5** (1–4)

[a]Patient 8 received TAG at 12 mcg/kg during treatment at first relapse, and at 7 mcg/kg at second relapse.

Tagraxofusp treatment was associated with promising efficacy and a manageable safety profile in pediatric and young adult patients with BPDCN

Table 2. Patient Case Details

Patient #	Age (Years)/ Sex	Prior Treatment	TAG Treatment	Best Response	Safety	Status as of Publication	Survival From Start of TAG Treatment
1L Patients							
1	21/F	NA	4 cycles (12 mcg/kg), D1–5	SD	Headache, hot flashes, fatigue, mouth sores	Was recommended hyperCVAD + Ven followed by SCT, but died prior to receiving SCT (PD)	11.5 months
2	20/M	NA	**1L:** 3 cycles (12 mcg/kg), D1–5 **2L:** 2 cycles (12 mcg/kg), D4–6 (TAG + Aza + Ven)	**1L:** SD **2L:** CR; bridged to SCT	Low albumin, transaminitis (AST 37; ALT 130), G2 CLS (treated, resolved after 4 days), G3 headache, and G3 elevated LFTs after C1D2	Alive post-MSD SCT	16+ months
3	16/F	NA	4 cycles (12 mcg/kg), D1–5 (+ IT chemotherapy)	CR; bridged to SCT	No AEs reported	Alive after SCT	33+ months
4	16/F	NA	4 cycles (12 mcg/kg), D1–5	Good PR with skin MRD (biopsy positive); bridged to allo-SCT[a]	No AEs reported	Alive post-haploidentical SCT	7+ months
5	15/F	NA	4 cycles (12 mcg/kg), D1–5	Morphologic CR; histologic evaluation after C3 showed 4-5% blasts	Rash (G1), CLS (G2), and transaminitis (G3) during C1	CR (BM) following 1 cycle FLAG-Myocet®; disease-free post-MUD SCT	6+ months
R/R Patients							
6	15/F	ADE induction; HDAC + etoposide intensification	1 cycle (12 mcg/kg), D1–5	PD; developed CNS disease	Low albumin	HCVAD + Ven and twice-weekly LP + IT; molecular remission achieved, followed by SCT	36+ months
7	10/F	Chemotherapy per AML protocol and SCT (relapsed)	2 cycles (12 mcg/kg), D1–5, as part of induction prior to second SCT	SD; bridged to SCT	No AEs reported	Second SCT complicated by mild GVHD that resolved; currently no evidence of disease (BM and PET/CT negative 1 year post-SCT)	12+ months post-SCT
8	2/F	ALL-type chemotherapy regimen[b]; relapsed during maintenance. COG AALL07P1 reinduction block 1	**2L:** 2 cycles (12 mcg/kg) D1–5[c] **3L:** 1 cycle (7 mcg/kg) D1-3 (TAG + Aza + Ven)	**2L:** minor response[d]; bridged to SCT **3L**[e]**:** PD	**2L:** transaminitis after C1 (AST 216; ALT 87), normalized in C2 **3L:** transaminitis (AST 216; ALT 128)	Alive in hospice care, currently no evidence of disease (BM and CBC normal)	6+ months

[a]Following a single course of FLAG-IDA + local radiotherapy on residual lesion. [b]Based on COG AALL1131. [c]Patient required albumin infusions prior to TAG. [d]Based on BM morphology and flow. [e]Patient relapsed 7 months post-SCT.

Safety

- Safety outcomes for all patients are summarized in **Table 2**
- Capillary leak syndrome occurred in 2/8 (25%) patients, both grade 2, and both were successfully managed with TAG dose interruptions and treatment of symptoms (albumin, furosemide, and dopamine treatment)
- Other AEs reported:
  - Low albumin occurred in 2/8 (25%) patients and transaminitis was reported in 3/8 (37.5%) patients
  - Headaches were reported in 2/8 (25%) patients (including one grade 3)
- Three of 8 (37.5%) patients reported no AEs
- All AEs occurred during cycle 1

Efficacy

- Efficacy outcomes for all patients are summarized in **Table 3**: three of 5 (60%) 1L patients achieved a CR after treatment with TAG
  - One patient had extensive disease with skin, bone marrow, and central nervous system involvement prior to treatment, all of which resolved

Bridging to Stem Cell Transplantation (SCT)

- Five patients were bridged to SCT after treatment with TAG
  - One patient received TAG as 1L
  - One patient received TAG, azacitidine, and venetoclax as second-line treatment
  - One received a single course of FLAG-IDA (fludarabine, high-dose cytarabine, idarubicin, and granulocyte colony-stimulating factor) + local radiotherapy
  - Two patients received TAG for R/R disease
- Seven of 8 patients are alive at the time of this analysis

Table 3. Best Response to TAG

Outcomes	1L BPDCN n=5	R/R BPDCN n=3	All Patients N=8
Response to TAG, n (%)			
CR	**3** (60)	**0**	**3** (38)
PR	**1** (20)	**0**	**1**
MR	**0**	**1** (33)	**1** (13)
SD	**1** (20)	**1** (33)	**2** (25)
PD	**0**	**1** (33)	**1** (13)
Bridged to SCT, n (%)	**3** (60)	**2** (67)	**5** (63)

CONCLUSIONS

- TAG therapy in these 8 pediatric/young adult patients showed promising antitumor efficacy with 3/8 (38%) patients achieving a CR
- Five of 8 (63%) patients were bridged to SCT, suggesting that TAG therapy can be used to bridge to SCT in young patients as well as adults
- TAG had a manageable safety profile in this pediatric/young adult population with a similar AE profile to that seen in the adult population[8]
- TAG was used in combination with other therapies in 2 patients, 1 of whom had a CR and was bridged to SCT, suggesting that TAG may be effective as part of a combination therapy regimen in pediatric patients
  - TAG in combination with azacitidine and/or venetoclax is currently being tested in a phase 1 clinical trial of adult patients with AML or BPDCN (NCT03113643)[10]
- Seven of 8 patients are alive at the time of this analysis

Abbreviations in Tables/Figure: 1L, first-line; 2L, second-line; 3L, third-line; ADE, cytarabine, daunorubicin, etoposide; AE, adverse event; ALL, acute lymphocytic leukemia; allo, allogeneic; ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; Aza, azacitidine; BM, bone marrow; BPDCN, blastic plasmacytoid dendritic cell neoplasm; C, cycle; CBC, complete blood count; CLS, capillary leak syndrome; CNS, central nervous system; COG, Children's Oncology Group; CR, complete response; D, days; EMA, European Medicines Agency; F, female; FLAG-IDA, fludarabine, high-dose cytarabine, idarubicin, and granulocyte colony-stimulating factor; G, grade; GVHD, graft-versus-host disease; hyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; HDAC, histone deacetylase; IT, intrathecal; LFT, liver function tests; LN, lymph node; LP, lumbar puncture; M, male; MRD, minimal residual disease; MR, minor response; MSD, matched sibling donor; MUD, matched unrelated donor; NA, not applicable; PET/CT, positron emission tomography/computed tomography; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SCT, stem cell transplantation; SD, stable disease; TAG, tagraxofusp; US FDA, United States Food and Drug Administration; Ven; venetoclax.

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