Tagraxofusp in Blastic Plasmacytoid Dendritic Cell Neoplasm With/Without Central Nervous System Involvement and Intrathecal Chemotherapy as Primary Treatment or Prophylaxis: an Italian Experience

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INTRODUCTION

- Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a highly aggressive orphan hematologic malignancy derived from plasmacytoid dendritic cells (pDCs) that overexpress CD123, the interleukin-3 (IL-3) receptor alpha subunit[1,2]
- BPDCN is typically characterized by skin, bone marrow, and lymph node involvement at presentation[3]
- Despite initial response at the medullary and skin level, patients often relapse with central nervous system (CNS) involvement, in part due to the CNS acting as a sanctuary for systemic chemotherapy[4]
- The precise frequency of CNS involvement is currently unknown. Retrospective studies have found CNS involvement in approximately 10% of patients at diagnosis and in 30% at time of first relapse[1,5]
- A recent small prospective study using flow cytometry showed higher incidence of CNS involvement both at diagnosis (60%) and relapse (100%), suggesting occult CNS involvement in asymptomatic patients[6]
- Achieving complete clearance of disease in the meningeal compartment is essential. Intrathecal (IT) chemotherapy is administered both as prophylactic and primary treatment, and its use in combination with systemic treatment can lead to long-term remissions[6,7]
- Currently, there is no standard treatment for patients with CNS+ BPDCN and new approaches that combine CNS-directed prophylaxis or treatment and targeted systemic therapy may improve long-term outcomes for patients with BPDCN, especially for those with occult CNS involvement
- Tagraxofusp (TAG) is a first-in-class CD123-targeted therapy consisting of recombinant human IL-3 fused to a truncated diphtheria toxin payload[8]
- TAG was approved by the US Food and Drug Administration for the treatment of patients ≥2 years of age with newly diagnosed or relapsed/refractory BPDCN in 2018,[9] and in 2021 by the European Medicines Agency (EMA) for the treatment of BPDCN in first-line adult patients[10]
- In the pivotal trial (NCT02113982), although CNS screening was not mandatory, TAG treatment resulted in durable long-term responses with a well-characterized and manageable safety profile in adult patients with BPDCN[11,12]
  - Recent analyses of a BPDCN database and current National Comprehensive Cancer Network guidelines recognize that CNS screening is increasingly important[13,14]
- Before EMA approval, TAG first became available in Europe in August 2019 via an expanded access program (EAP) for the treatment of patients with BPDCN, including those with baseline CNS involvement
- Herein, we report a single-center experience of TAG therapy in patients with BPDCN with or without CNS involvement who were enrolled in the TAG EAP
  - The aim of this study was to determine whether CNS prophylaxis or treatment combined with systemic TAG therapy impacts patient prognosis and efficacy of systemic TAG therapy

Tagraxofusp with IT chemotherapy in patients with BPDCN was associated with promising efficacy in patients with CNS disease, with no unexpected safety events

METHODS

- Retrospective analysis of patients with BPDCN at our institution who were enrolled in the European TAG EAP from August 2019 to December 2021
- For inclusion in the EAP, patients required a BPDCN diagnosis confirmed by hematopathology with biomarkers, including positivity for CD123, CD4, and CD56
- CNS involvement was assessed by lumbar puncture, and presence of BPDCN cells in cerebrospinal fluid (CSF) was confirmed by cytopathology and 8-color flow cytometry for identification of CD123+ pDCs
- All patients were treated with intravenous TAG infusions at 12 mcg/kg once daily on days 1–5 of a 21-day cycle for 1 to 4 cycles, depending on response and the potential to bridge to hematopoietic stem cell transplant (HSCT)
- Patients were hospitalized during the first cycle of TAG. In subsequent cycles, TAG was administered in an outpatient setting if no severe complications occurred during the first cycle
- IT chemotherapy consisted of cytarabine and dexamethasone ± methotrexate and was administered at each cycle either as prophylaxis for patients without CNS involvement or as primary-intention treatment in patients with CNS+ disease
- Data were collected through retrospective chart review and summarized descriptively
- Efficacy assessments included CSF examination for CNS response, tumor response, and survival. Tumor response criteria were the same used for the pivotal trial[11]
- For safety assessments, adverse events (AEs) were monitored, and AE severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0

RESULTS

Patients

- Clinical data from 5 patients with BPDCN who were enrolled in the TAG EAP at our institution are presented
- The median age was 64 years (range 16–72) and most patients were male (60%) (**Table 1**)
- All patients received TAG as first-line treatment for BPDCN
- The median number of TAG cycles received was 3 (range 1–4). All patients received TAG at 12 mcg/kg
- Three patients received IT chemotherapy as primary-intention treatment and 2 patients as prophylaxis
- Individual case details for each patient are presented in the **Figure** and **Tables 2–4**

Table 1. Main Baseline Patient Characteristics and TAG Treatment

Characteristic	Patients N = 5
Median age, years (range)	**64** (16–72)
Sex, n (%)	
Female	**2** (40)
Male	**3** (60)
Disease involvement, n (%)	
Skin	**5** (100)
Bone marrow	**4** (80)
CNS	**3** (60)
TAG treatment, n (%)	
First line	**5** (100)
Relapsed/refractory	**0** (0)
Median TAG cycles (range)	**3** (1–4)

Figure. Patient Cases: BPDCN at Presentation

Patient 1
- 51-year-old male
- Presented with skin, BM, and CNS involvement
- CNS involvement assessed by CSF physical-chemical, flow cytometric, and microscopic examination
- Absolute WBC count in CSF of 11.2 cells/mL
- Neurologic symptoms included confusion and spatial-temporal disorientation

Patient 2
- 71-year-old female
- Presented with skin, BM, lymph node, and CNS involvement
- CNS involvement assessed by CSF physical-chemical and flow cytometric examination
- Absolute WBC count in CSF of 4.16 cells/mL
- Absence of neurologic symptoms

Patient 3
- 72-year-old male
- Presented with skin, BM, oropharynx, and CNS involvement
- CNS involvement assessed by CSF physical-chemical and flow cytometric examination
- Absolute WBC count in CSF of 2.4 cells/mL
- Absence of neurologic symptoms

CNS+

CNS–

Patient 4
- 16-year-old female
- Presented with skin lesions; CNS involvement was excluded
- CNS involvement assessed by CSF physical-chemical and flow cytometric examination
- Absolute WBC count in CSF of 1 cell/mL

Patient 5
- 64-year-old male
- Presented with skin and BM involvement; CNS involvement was excluded
- CNS involvement assessed by CSF physical-chemical and flow cytometric examination
- Absolute WBC count in CSF of 0.8 cells/mL

Treatment

Table 2. Treatment

Patient No.	Age (Years)/ Sex	Treatment	
		TAG	IT
1	51/M	3 cycles (12 mcg/kg), D1–5	MTX 12.5 mg + cytarabine 50 mg + DEX 4 mg, 4 cycles
2	71/F	4 cycles (12 mcg/kg), D1–5	MTX 12.5 mg + cytarabine 50 mg + DEX 4 mg, 5 cycles
3	72/M	1 cycle (12 mcg/kg), D1–5	Cytarabine 50 mg + DEX 4 mg, 3 cycles
4	16/F	4 cycles (12 mcg/kg), D1–5	MTX 12 mg + cytarabine 30 mg + DEX 4 mg, 4 cycles
5	64/M	3 cycles (12 mcg/kg), D1–5	Cytarabine 50 mg + DEX 4 mg, 1 cycle

Safety

- Capillary leak syndrome (CLS) was the most common AE, occurring in 4/5 patients (grade [G]1, n = 1; G2, n = 2; G4, n = 1); all cases resolved
- Other AEs reported: pulmonary aspergillosis (n = 1) and sepsis (n = 1)
- There were no AEs associated with the IT chemotherapy

Table 3. Summary of CLS Events

Patient No.	Age (Years)/Sex	Grade	Outcomes
1	51/M	G1	Resolved
2	71/F	G2	Resolved
3	72/M	G4	Resolved
4	16/F	NA	NA
5	64/M	G2	Resolved

Efficacy

- All patients achieved a response, irrespective of baseline CNS involvement (**Table 4**)
- Two patients, both without CNS involvement, were bridged to HSCT
- All 5 patients are alive at the time of this analysis

Table 4. Efficacy Outcomes

Patient No.	Age (Years)/ Sex	Response		HSCT	Subsequent Treatment	OS From Diagnosis (mo)
		BPDCN	CNS			
1	51/M	PR after 1 TAG cycle, sustained for 2 mo	CR after 1 IT cycle, sustained for 8 mo[c]	No	HyperCVAD	10
2	71/F	Morphologic CR with MRD positivity after 2 TAG cycles, sustained for 6 mo	CR after 1 IT cycle, sustained for 4 mo[c]	No	COMP	11
3	72/M	PR after 1 TAG cycle, response ongoing	CR after 1 IT cycle, sustained for 4 mo	No	No	7
4	16/F	PR[a] after 4 TAG cycles, sustained for 1 mo	NA	Yes	FLAG-IDA, HSCT[d]	12
5	64/M	CR[b] after 3 TAG cycles, sustained until HSCT	NA	Yes	HSCT	32

[a]Skin lesion size reduction with evidence of persistence of disease. [b]The patient is maintaining CR post HSCT at last available follow-up. [c]The patient relapsed with CNS involvement in addition to systemic disease. [d]After FLAG-IDA the patient proceeded (in CR) to allogeneic HSCT (haploidentical donor); current status post HSCT is CR.

CONCLUSIONS

- These preliminary results confirm the feasibility of IT chemotherapy in combination with systemic TAG therapy
- Baseline CNS involvement did not appear to impact TAG efficacy, with 2 (40%) patients achieving complete response (CR) and 3 (60%) partial response
  - Two patients were bridged to HSCT
- IT chemotherapy effectively cleared disease from the CSF, with all 3 patients with baseline CNS involvement achieving CNS CR
- No unexpected safety events occurred when TAG was administered concomitantly with CNS prophylaxis or treatment
  - CLS, when reported, was managed with treatment and subsequently resolved
- Despite the limited number of patients analyzed, this single-center experience shows a high frequency of patients with CNS+ BPDCN at the time of diagnosis and suggests that patients should be routinely checked for CNS involvement
  - Analysis of CSF by flow cytometry for CD123+ cells has higher sensitivity than physical-chemical or microscopic techniques and allows identification of patients with minimal CNS involvement

Abbreviations in Tables/Figure: BM, bone marrow; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CLS, capillary leak syndrome; CNS, central nervous system; COMP, cyclophosphamide, non-pegylated liposomal doxorubicin, vincristine, prednisone; CR, complete response; CSF, cerebrospinal fluid; D, day; DEX, dexamethasone; F, female; FLAG-IDA, fludarabine, high-dose cytarabine, idarubicin, and granulocyte colony-stimulating factor; G, grade; HSCT, hematopoietic stem cell transplant; hyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; IT, intrathecal; M, male; mo, months; MRD, minimal residual disease; MTX, methotrexate; NA, not applicable; OS, overall survival; PR, partial response; TAG, tagraxofusp; WBC, white blood cell. **REFERENCES: 1.** Feuillard J, et al. *Blood.* 2002;99:1556-1563. **2.** Garnache-Ottou F, et al. *Blood Adv.* 2019;3:4238-4251. **3.** Guru Murthy GS, et al. *Leuk Res.* 2018;73:21-23. **4.** Pemmaraju N, et al. *Blood Adv.* 2022;6:3027-3035. **5.** Martín-Martín L, et al. *Oncotarget.* 2015;6(22):19204-19216. **6.** Martín-Martín L, et al. *Oncotarget.* 2016;7(9):10174-10181. **7.** Pagano L, et al. *Haematologica.* 2013;98(2):239-246. **8.** Frankel AE, et al. *Blood.* 2014;124(3):385-392. **9.** ELZONRIS® (tagraxofusp-erzs) [prescribing information]. New York, NY: Stemline Therapeutics; 2018. **10.** ELZONRIS [summary of product characteristics]. Amsterdam, the Netherlands: Stemline Therapeutics B.V.; 2021. **11.** Pemmaraju N, et al. *N Engl J Med.* 2019;380(17):1628-1637. **12.** Pemmaraju N, et al. *HemaSphere.* 2021;5:171. Abstract EP427. **13.** Pemmaraju N, et al. *Blood.* 2021;138(15):1373-1377. **14.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Acute Myeloid Leukemia v1.2022. **DISCLOSURES: G. Rivoli:** Nothing to disclose. **G. Beltrami:** Nothing to disclose. **A.M. Raiola:** Nothing to disclose. **A. Dominietto:** Nothing to disclose. **M. Riggi:** Employee of Menarini Stemline. **E. Angelucci:** Consultancy agreement with Menarini Stemline, honoraria from Novartis and Celgene, involvement in local advisory boards for bluebird bio, Glaxo, Gilead, and Roche, and participation in DMC for Celgene, Vertex Pharmaceuticals Inc., and CRISPR Therapeutics. **ACKNOWLEDGMENTS:** Editorial and medical writing assistance was provided by Iratxe Abarrategui, PhD, CMPP, from Aptitude Health, The Hague, the Netherlands, and funding of this was supported by Stemline Therapeutics Inc., New York, NY. The authors are fully responsible for all content and editorial decisions for this poster.