ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Research Article

Hematologic Malignancies in Temozolomide-Treated Metastatic Pancreatic Neuroendocrine Tumors

Nicole Balmaceda*, Tyler Mouw, Sunil Abhyankar, Heather Male, Janet Woodroof and Joaquina Baranda

University of Kansas Cancer Center, Kansas City, United States

***Corresponding Author**: Nicole Balmaceda, University of Kansas Cancer Center, Kansas City, United States.

Received: February 05, 2020; **Published:** March 03, 2020

Abstract

Background and Purpose: Metastatic pancreatic neuroendocrine tumors (PNET) are generally not curable; however, some patients may have prolonged survival. New developments demonstrating improved clinical outcomes in these patients treated with temozolomide (TMZ) resulted in its off-label use in National Comprehensive Cancer Network guidelines. However, serious hematologic adverse events (AEs) like agranulocytosis, lymphopenia, and aplastic anemia are not uncommon. At the University of Kansas Cancer Center (KUCC), 3 patients with history of TMZ-treated metastatic PNET developed hematologic malignancies. The purpose of this study is to determine the incidence of secondary malignancies (SM) in this patient population.

Methods: A systematic review of all known clinical trials, case reports, and other relevant literature regarding PNET and TMZ published before September 2017 was conducted using PubMed, Embase, Cochrane Library, and the FDA Adverse Event Reporting System (FAERS).

Results: 38 publications and 8,215 cases reported from FAERS were analyzed. No publications reported SM. The 3 patients with TMZ-treated metastatic PNET identified at KUCC are as follows: 1) 29-year-old female who developed acute myeloid leukemia with cytogenetics consistent with therapy-related leukemia. 2) 80-year-old male who developed diffuse large B-cell lymphoma. 3) 12-year-old male who developed high-grade T-cell lymphoblastic lymphoma. All these patients succumbed to their hematologic malignancies, and not the underlying PNET.

Conclusion: Although we observed 3 cases at KUCC, this retrospective review did not find any cases of SM in TMZ-treated metastatic PNET. We believe that the leukemogenic potential of TMZ is underreported. It is important for treatment guidelines to address this risk in the decision to pursue TMZ treatment.

Keywords: *Metastatic Pancreatic Neuroendocrine Tumor; Temozolomide; Secondary Malignancy; Leukemia; Lymphoma*

Introduction

Metastatic pancreatic neuroendocrine tumors (PNET) are generally not curable; however, some patients may have prolonged survival. Until recently, metastatic PNET were primarily managed with somatostatin-analogs. New developments demonstrating therapeutic value of temozolomide (TMZ) in these patients resulted in its off-label use in National Comprehensive Cancer Network guidelines. Given alone, or in combination with other therapies, TMZ is associated with improved clinical outcomes. However, serious hematologic adverse events (AEs) like agranulocytosis, lymphopenia, and aplastic anemia are not uncommon. At the University of Kansas Cancer Center (KUCC),

there were 3 patients who developed hematologic malignancies after treatment with TMZ for metastatic PNET. Secondary malignancy in patients with TMZ-treated metastatic PNET have not been well-studied. To determine how common secondary malignancies (SM) are in this patient population, our group conducted a systematic review of the literature.

Objective of the Study

The objective of this study is to determine the prevalence of SM in patients treated with TMZ for PNET.

Methods

A systematic review of all known clinical trials, case reports, and other relevant literature regarding PNET and TMZ published before September 2017 was conducted using PubMed, Cochrane Library and the FDA Adverse Event Reporting System (FAERS).

Results

We analyzed 38 publications (Table 1) and 8,215 cases reported from FAERS. AEs ranged from agranulocytosis to myelodysplastic syndrome. No publications reported any SM. The 3 patients identified at KUCC are as follows: 29-year-old female with TMZ-treated metastatic PNET developed acute myeloid leukemia with cytogenetics consistent with therapy-related leukemia. 80-year-old male with TMZ-treated metastatic PNET developed diffuse large B-cell lymphoma. 12-year-old male with TMZ-treated metastatic PNET developed high-grade T-cell lymphoblastic lymphoma. All these patients succumbed to their hematologic malignancies, and not the underlying PNET.

Study	Regimen	# PNET or GEP/NET	# 2° cancers
Abbasi., *et al*. 2014	CAP 600 mg/m^2 x 2/d, d1-14 TMZ 150-200 mg/m^2:2/d, d10-14, q4wk	14 PNET/21	0
Boutzios., *et al*. 2016	TMZ-based therapy	115 PNET	0
Bracht., *et al*. 2008	TMZ 75-200 mg/m^2/d, d10-14, q4wk	1 PNET	0
Chan., *et al*. 2012	TMZ 150 mg/m^2/d, d1-7, d15-21 BVZ 5 mg/kg d1, d15, q4wk	15 PNET/34	0
Chan., *et al*. 2013	TMZ 150 mg/m^2/d, d1-7, d15-21, everolimus 5-10 mg/d q4wk max duration: 6 months	43 PNET/43	0
Chaves., *et al*. 2016	CAP 750 mg/m^2 x 2/d, d1-14 TMZ 150-200 mg/m^2 :2/d, d10-14, q4wk	4 PNET/10	0
Cives., *et al*. 2016	CAP 750 mg/m^2 x 2/d, d1-14 TMZ 200 mg/m^2/d, d10-14, q4wk	143 PNET	0
Claringbold., *et al*. 2016	CAP 1500 mg/m^2/d, d1-14 TMZ 200 mg/m^2/d, d10-14, q4wk ^{177}Lu-octreotate 7.9 GBq d5, q8wk (4 cycles)	30 PNET	0 (2 MDS)
Crespo., *et al*. 2017	CAP 750-1000 mg/m^2 x 2/d, d1-14 TMZ 150-200 mg/m^2/d, d10-14, q4wk	46 PNET/65	0

Cros., *et al*. 2016	CAP 750 mg/m^2 x 2/d, d1-14 TMZ 150-200 mg/m^2/d, d10-14, q4wk	43 PNET	0
De Divitiis., *et al*. 2016	Metronomic TMZ 75 mg/m^2/d – one-week-on/one-week-off)	1 PNET	0
Ekeblad., *et al*. 2007	TMZ 200 mg/m^2/d, d1-5, q4wk	12 PNET/36	0
Fine., *et al*. 2005	CAP 1500 mg/m^2/d, d1-14 TMZ 150-200 mg/m^2/d, d10-14, q4wk	10 NET	0
Fine., *et al*. 2014	CAP 1500 mg/m^2 :2/d, d1-14 TMZ 150-200 mg/m^2 :2/d, d10-14, q4wk	11 PNET/ 28	0
Fine., *et al*. 2013	CAP 600 mg/m^2 x 2/d, d1-14 TMZ 150-200 mg/m^2 :2/d, d10-14, q4wk	7 PNET/18	0
Ganetsky., *et al*. 2012	CAPTEM	16 PNET/20	0
Isacoff., *et al*. 2006	CAP 1000 mg x 2/d, d1-14 TMZ 150-200 mg/m^2/d, d10-14, q4wk	17 PNET	0
Jia., *et al*. 2016	CAPTEM	20/28 NET	0
Koumarianou., *et al*. 2013	Metronomic TMZ 100 mg/d, d1-21 BVZ 7.5 mg/kg d1, q3wk	7 PNET/15	0

Table 1: *Summary of literature review.*

Discussion

In our study, there were no published reports of SM in TMZ-treated PNET, yet, SM and MDS in TMZ-treated brain tumors are well-documented. Various studies have shown cytogenetics with therapy-related MDS or leukemia (t-MDS/t-AML) in SM in TMZ-treated brain tumors [1-5]. In this study, 3 TMZ-treated PNET patients were found to have MDS. Cytogenetics available in 1 patient showed abnormalities in chromosome 7, commonly seen in t-MDS/t-AML.

At KUCC, we report 3 patients who developed leukemia or lymphoma after TMZ for PNET (Table 2). In 1 patient, cytogenetics showed translocation abnormalities in chromosomes 1 and 7, also consistent with t-AML. Figure 1 shows liver biopsy and bone marrow of this patient. All 3 patients at KUCC had metastatic PNET and died due to their hematologic malignancies. TMZ may increase the risk of SM in patients treated for PNET. The leukemogenic potential of TMZ may be underreported. TMZ dosing in PNET is more extensive compared to other malignancies. With increasing use of TMZ in the treatment of PNET, it is anticipated that cases of SM will soon emerge in the literature.

Pt age at dx/ sex	TMZ Dose/Duration	Cytogenetics	2^o Malignancy	Outcome/Comments
29yo F	TMZ 150 mg/m^2/d, d1-7, d15-21 + thalidomide 50 mg/d 36 months	46, XX, inv (3) (q21q26.2) 46, XX, sl,del (9)(q13) 46, XX, der(1;7) (q10;p10), inv(3)(q21q26.2)	Acute Myeloid Leukemia (AML)	• Had partial response of PNET w/ TMZ • Leukemia, aggressive, refractory to multiple chemotherapy regimens • Translocation 1;7 is often seen in secondary or therapy-related AML • Died of AML 1 year after that dx

80yo M	TMZ 150 mg/m^2/d, d1-7, d15-21 + thalidomide 50 mg/d 9 months	46, XY	Diffuse Large B-Cell Lymphoma	• Had stable disease of PNET w/ TMZ • Lymphoma refractory to multiple treatment regimens • Died of lymphoma 9 months after that dx
12yo M	TMZ + thalidomide	46, XY	T-Cell Lymphoblastic Leukemia	• Unknown TMZ dosage • Response of PNET, stable on Octreotide • Underwent chemotherapy for leukemia with involvement of multiple lymph nodes, liver, CSF • Died from extensive leukemia

Table 2: *Patients with Hematologic Malignancy After TMZ at KUCC.*

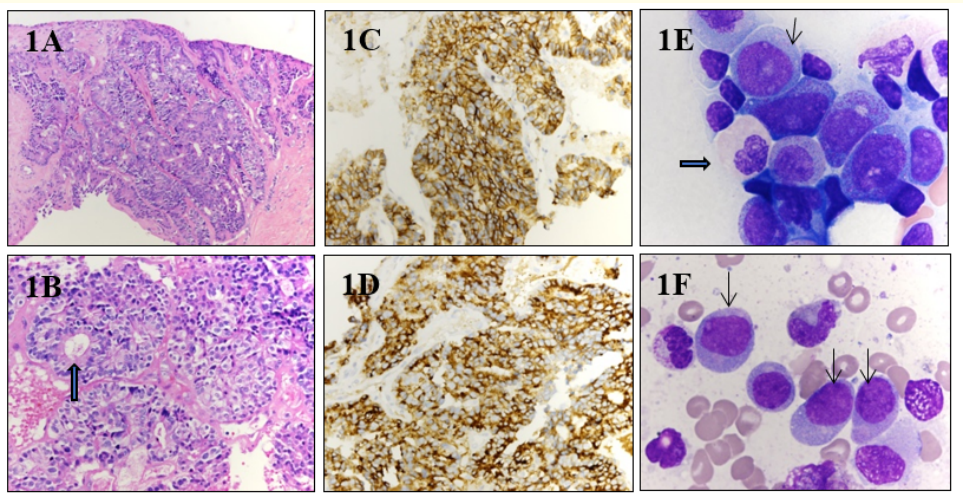

Figure 1: *29-year-old female with AML after TMZ for PNET described in table 2. Liver needle biopsy showing NET (A) with undifferentiated cells and rosette (B). Liver Biopsy positive for CD56 (C) and chromogranin (D), markers for NET. Bone marrow with 30% blasts and dysplastic features (E). Bone marrow aspirate with increased blasts and dysplastic neutrophil (F).*

Conclusion

Many patients are benefiting from personalized medicine, specifically targeted therapy. In PNET, traditional nonspecific chemotherapy such as TMZ are still in use with improved clinical outcomes. With the new age of personalized medicine, peptide receptor radionucleotide therapy (PRRT) has become increasingly popular as the radiopeptides are selective in damaging certain types of cancer cells. Clinical trials evaluating the combination of typical chemotherapy (temozolomide and capecitabine) and 177-Lu-DOTATOC are in investigation.

At one university, there were 3 patients who developed hematologic malignancies after treatment with TMZ for metastatic PNET. Secondary malignancy in patients with TMZ-treated metastatic PNET have not been well-studied. PRRT has been reported to cause hemato-

logic malignancies. The combination of TMZ and PRRT may prove efficacious in treating PNET, but may also pose dangers if combination therapy increases the risk of secondary malignancies.

It is an exciting time as new novel therapies are being used in practice, but we should remain vigilant of the potential SM associated with TMZ and other leukemogenic therapies including other cytotoxic chemotherapy and PRRT for PNET.

Although we observed 3 cases at KUCC, this retrospective review did not find any cases of SM in TMZ-treated metastatic PNET. We believe that the leukemogenic potential of TMZ is underreported. It is important for treatment guidelines to address this risk in the decision to pursue TMZ treatment. We call for consideration of updating treatment guidelines for TMZ in PNET, specifically, indications for initiation of treatment, patient selection, duration of treatment, and surveillance for long-term adverse events, especially for those patients anticipated to have indolent disease and long survival from their PNET. Investigations designed to personalize treatment based on molecular biology may address some of these questions.

Acknowledgements

Special thanks to Dr. Stephen Williamson, Dr. Anusha Vallurupalli, and Dr. Paul Danese.

Disclosures

J. Baranda: Research-Astellas,R egeneron, Exelixis, Tolero, Pfizer, Incyte, Xencor; Stocks-Hylapharm, Zymeworks.

Bibliography

1. Chou KN., *et al*. "Temozolomide-Related Acute Lymphoblastic Leukemia with Translocation (4;11)(Q21;Q23) in a Glioblastoma Patient". *Journal of Clinical Neuroscience* 21.4 (2014): 701-704.

2. Tan CW., *et al*. "Treatment-Related Acute Myeloid Leukaemia after Temozolomide for Glioblastoma Multiforme". *Annals, Academy of Medicine, Singapore* 43.6 (2014): 334-337.

3. Momota H., *et al*. "Secondary Hematological Malignancies Associated with Temozolomide in Patients with Glioma". *Neuro-Oncology* 15.10 (2013): 1445-1450.

4. Ogura M., *et al*. "Temozolomide May Induce Therapy-Related Acute Lymphoblastic Leukaemia". *British Journal of Haematology* 154.5 (2011): 663-665.

5. Shaikh AJ and N Masood. "Acute Lymphoblastic Leukemia Subsequent to Temozolomide Use in a 26-Year-Old Man: A Case Report". *Journal of Medical Case Reports* 4 (2010): 274.

Volume 7 Issue 4 April 2020
©All rights reserved by Nicole Balmaceda., *et al.*