

Aggressive Grade 2 Neuroendocrine Tumor Salvaged by Temozolomide-Based Therapy: A Case Report and Literature Review

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Abstract

We are reporting a 59-year-old woman with a grade 2 (G2) moderately differentiated metastatic neuroendocrine (NET) tumor of unknown origin with Ki67 rate of 15%. First-line treatment with etoposide and cisplatin failed with evidence of rapid disease progression. However, second-line therapy with temozolomide associated to capecitabine proved an unexpected efficacy resulting in a consistent partial response. Immunohistochemistry staining for O-6-methylguanine-DNA methyltransferase (*MGMT*) expression was performed retrospectively and was negative, which could predict response to temozolomide. Systematic treatment strategies of non-well differentiated NETs are reviewed, as well as the role of *MGMT* as predictive factor for the efficacy of temozolomide.

Keywords: Neuroendocrine tumor; Moderately differentiated; Temozolomide; *MGMT*

Introduction

Computed Neuroendocrine tumors (NETs) have been recently classified by World Health Organization (WHO) criteria into well-differentiated neuroendocrine tumors grade 1 (WD-NETs G1), well-differentiated neuroendocrine tumors grade 2 (WD-NETs G2), and poorly differentiated neuroendocrine tumors (PD-NETs G3) [1]. G1 NETs classification derived from a mitotic count of less than 2/10 high-power field (HPF) and/or a Ki-67 index of less than 3%. In G3 NETs, the mitotic count usually exceeds 20/10 HPF and/or the Ki-67 index exceeds 20%. While G2 represent the group of tumors that fall right between G1 and G3 tumors with a mitotic count ranging from 2 to 20/10 HPF and/or Ki-67 that falls between the two extreme levels of 2% and 20%.

Treatment guidelines based on those histological classifications have been recommended mainly for the grade 1 where somatostatin analogs are the mainstay therapy, and grade 3 tumors where the aggressive combination of platinum and etoposide is the standard of care. There is a lack of consensus on the optimal treatment strategy for grade 2 tumors, and only limited data from retrospective studies is available in the literature.

We report a case of highly aggressive and multi-metastatic NET disease classified as G2 tumor, where resistance to the combination of etoposide and cisplatin was encountered contrasting with a sensitivity to temozolomide-based therapy.

Case Report

A 59-year-old female presented to the office complaining of atypical back pain. The pain started a few months ago, increasing gradually in intensity, along with loss of appetite and 10% loss of her weight. The spine MRI showed multiple lytic bony lesions involving the dorsal and lumbo-sacral spine. Total body scan revealed multiple subcentimeter pulmonary nodules as well as multiple secondary hepatic lesions and bilateral adrenal suspicious enlargement. The patient underwent a transcutaneous biopsy of the adrenal gland. Histomorphological examination revealed monomorphic cell nuclei and lack of necrosis. Ten mitosis per 10 HPF were counted and Ki67 was 15%. On immunohistochemistry (IHC), the tumor was highly positive for synaptophysin and chromogranin receptor, moderately positive for CK7, low positive for TTF-1, and negative for CK20. The diagnosis of a moderately

differentiated (G2) neuroendocrine tumor was confirmed. Gallium scan showed the same pattern of disease extension but failed to identify a primary lesion. Chromogranin serum assessment was not done. 24-hour urine 5-hydroxyindoleacetic acid was within normal range. The patient received cytotoxic chemotherapy with etoposide 100 mg/m² intravenously (IV) on days 1 to 3 and cisplatin 75 mg/m² day 1 of a 21 day cycle for four cycles, associated with zoledronic acid 4 mg IV. Pain and weight loss increased after the second cycle, along with progression of the lesions by more than 75% on subsequent disease assessment. She received second-line therapy with temozolomide 150 mg/m² divided into two doses daily on days 1 to 5, and capecitabine 600 mg/m² orally twice daily on days 1-14 of a 21-day cycle. After the completion of her second cycle, the patient presented with a complete disappearance of her pain, regain of appetite and weight, as well as a decrease in disease extension of more than 30%. Actually, the disease remains in sustained partial response while the patient is receiving the eighth cycle. *MGMT* IHC was subsequently performed (Caris Life Sciences) and was negative (2% staining).

Discussion

Despite the heterogeneity of NETs, the diagnosis confirmation relies on IHC that reveals positivity for neuroendocrine markers such as synaptophysin and chromogranin. They may also be associated with specific symptoms related to peptide release, which differentiates functioning from nonfunctioning tumors.

The recommended treatment for PD-NETs G3 is chemotherapy using etoposide (VP 16) and cisplatin (CDDP) [2]. This treatment strategy is extrapolated from the efficacy of this regimen in extensive

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stage small cell lung cancer since 1991. At that time, Moertel et al. proved its efficacy in treating anaplastic neuroendocrine carcinomas of the lungs with an objective tumor regression of 67%, median progression free survival (PFS) of 9 months and median overall survival (OS) of 19 months [3]. In a subsequent study of 36 patients with advanced NETs (either poorly-differentiated histology or a rapidly progressing clinical course), second- or even third-line with cytotoxic chemotherapy cisplatin and etoposide yielded an overall radiologic response rate of 36% and a median OS of 19 months [4]. Furthermore, and with the same regimen, Mitry et al. reported a similar response rate (42%) and median OS of 15 months in a retrospective analysis of 41 patients with poorly differentiated NETs. Interestingly, only 1 of 11 patients with well-differentiated NET responded [5]. This was further analyzed in a recent retrospective study: The NORDIC NEC study, where 305 patients with advanced gastro-intestinal NETs were included. The authors concluded that patients with Ki-67 < 55% were less responsive to platinum-based chemotherapy but had longer survival [6].

In contrast to poorly differentiated NETs, the advanced or metastatic well-differentiated, slow growing (Ki-67 < 2%) NETs are treated with somatostatin analogs. The PROMID study, showed a statistically significant median PFS benefit of 14.3 months versus 6 months in favor of octreotide LAR [7]. Lanreotide, in the CLARINET study, was also associated with a significantly prolonged PFS with median not reached versus median of 18.0 months in the placebo arm [8]. However, there is a lack of effective cytoreductive regimens without substantial toxicity. Historically, streptozotocin (STZ), STZ ± doxorubicin or 5-fluorouracil (5-FU) were the only approved regimens for metastatic pancreatic NETs (PNETs). However, older studies were mostly retrospective, and the fact that they often lacked the use of strict radiographic criteria for response evaluation accounts for their low credibility. When RECIST indices were accurately utilized in recent studies, response rates ranged from 6 to 16%, and substantial grade 3/4 toxicities were observed [9].

Dacarbazine (DTIC), a member of the class of alkylating agents, was prospectively studied for metastatic PNETs as a high-dose single agent with an ORR of 34% [10]. Temozolomide (TMZ), which is an oral formulation of the first metabolite of DTIC has a more favorable toxicity profile. In the earliest reports in 2006, TMZ, in a phase 2 study, in combination with thalidomide produced a combined RR of 25% (45% in PNETs, 33% in pheochromocytomas and 7% in carcinoids) and a median PFS of 13.5 months. The major downside was significant toxicity where 69% of patients developed grade 3-4 lymphopenia, and 10% had opportunistic infections [11].

While single agent capecitabine did not succeed in providing a substantial activity in a small phase 2 study [12], its association with temozolomide proved to be an exciting combination. As a basic rationale, capecitabine induces DNA damage by incorporation of 5-FdUTP into DNA resulting in an inhibition of thymidylate synthase via 5-FdUMP and reducing thymidine pools. Thus, the addition of temozolomide and its effect on O⁶-alkylguanyl alkyl-transferase (O⁶-AGAT) is synergistically enhanced by capecitabine [13], which acts by depleting the DNA repair enzyme O⁶-methylguanine DNA methyltransferase (*MGMT*) making it more sensitive to the antiproliferative effects of temozolomide [14]. Kulke et al. published a retrospective analysis on *MGMT* expression in PNETs and carcinoid tumors. *MGMT* was found to be deficient in 50% of PNETs vs. 0% of carcinoid tumors, explaining the decreased tumor response to temozolomide in the latter [11]. This theoretical inefficacy was questioned by the fact that temozolomide and capecitabine combination, given in two daily dosages as proposed by Fine et al. in their pilot study of this regimen, resulted in a total response

rate of 61%, and a clinical benefit of 83.2% [15]. More recently, and using the same combination, an interim analysis of a phase II trial reported a response rate of 42%, including 8% CR and 58% SD with a median PFS of 22 months in patients with metastatic, well-to-moderately differentiated neuroendocrine tumors who had disease progression on long-acting octreotide (Sandostatin LAR), 60 mg, or who had negative octreotide scans, which is a negative prognostic factor [16].

Conclusion

At presentation, our patient with rapidly progressing disease behaved more like a G3 than a G2 disease, despite a Ki-67 of less than 20%. The combination of etoposide and cisplatin was thought to be the adequate strategy. However, the disease failed to respond and even progressed after three cycles. There was a strong unexpected partial response to second-line temozolomide and capecitabine. We subsequently performed immunostaining with anti-*MGMT* antibody on our patient's adrenal gland paraffin sections. The markedly low pattern of *MGMT* expression provides a clear explanation for the sensitivity of our patient's tumor to temozolomide. This finding, when correlated with Fine et al.'s hypothesis on *MGMT* depletion with the BID administration of temozolomide, might prove to be an important piece of the puzzle in order to determine the best first-line treatment to propose in patients with WD-NETs G2 tumors.

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