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Durable, exceptional response to temozolomide in a patient with extensive-stage small cell lung cancer (ES-SCLC) metastatic to brain

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ABSTRACT

Small cell lung cancer (SCLC) is an aggressive tumor that is frequently metastatic at diagnosis. Unfortunately, the repertoire of agents available to clinicians tasked with treating relapsed or refractory extensive-stage SCLC (ES-SCLC) is limited. We report the case of a patient with extensive, relapsed brain metastases who had an exceptional initial response to temozolomide (TMZ). We describe also the ongoing, durable complete radiographic response in excess of four years achieved via a combination of long-term therapy with TMZ and selectively deployed stereotactic radiosurgery (SRS). In spite of its recent addition to the National Comprehensive Cancer Network (NCCN) guidelines for relapsed SCLC, TMZ remains underutilized for this indication. This case supports the off-label use of TMZ in relapsed SCLC, especially those with central nervous system (CNS) metastases–for whom there are few to no available treatment options.

Clinical practice points

- FDA approved second-line on-label treatment options for SCLC are limited to only topotecan.
- CNS metastases are a common and therapeutically challenging site of relapsed and/or treatment refractory disease in SCLC.
- Here we report a case of a patient with multiple, extensive CNS-only relapses with a dramatic and durable response to oral temozolomide.
- We highlight the combinatorial use of temozolomide and selectively deployed SRS for patients with CNS relapse and prior WBRT.
- We provide a survey of the current literature regarding the response of neuroendocrine tumors, including SCLC, to temozolomide, including putative predictive biomarkers.

1. Introduction

In the United States, SCLC accounts for approximately 14% of lung cancers [1]. While response rates to frontline chemotherapy and radiation therapy are robust, the disease is characterized by rapid relapse and resistance to subsequent therapies resulting in uniformly poor overall survival. In the case of ES-SCLC, less than 5% of patients are alive at two years from diagnosis [2]. The propensity for SCLC patients to develop central nervous system (CNS) metastases further limits treatment options and prognosis. In the era prior to widespread use of prophylactic cranial irradiation (PCI), the estimated risk of CNS metastases was more than 50% [3]. While the adoption of PCI as a standard-of-care measure paired with advanced stereotactic radiosurgical techniques have made great strides in limiting and treating such metastases, the incidence of CNS metastases in SCLC remains high [4]. Unfortunately, the development of effective systemic therapies in recurrent SCLC has been slow and, currently, topotecan remains the only FDA-approved drug in second-line setting. In addition, for those patients who have previously received cranial irradiation or stereotactic radiosurgery, there are significant risks associated with retreatment, further limiting treatment options for patients with relapsed and/or refractory CNS disease.

TMZ is an orally administered DNA alkylating agent prodrug often used both concurrently and adjuvantly in combination with radiotherapy. It is FDA approved for the treatment of multiple primary brain malignancies including glioblastoma multiforme and refractory anaplastic astrocytoma. It has additional off-label indications in cutaneous T-cell lymphoma, Ewing's sarcoma, melanoma, CNS lymphoma, soft tissue sarcoma and advanced neuroendocrine (NE) tumors, including

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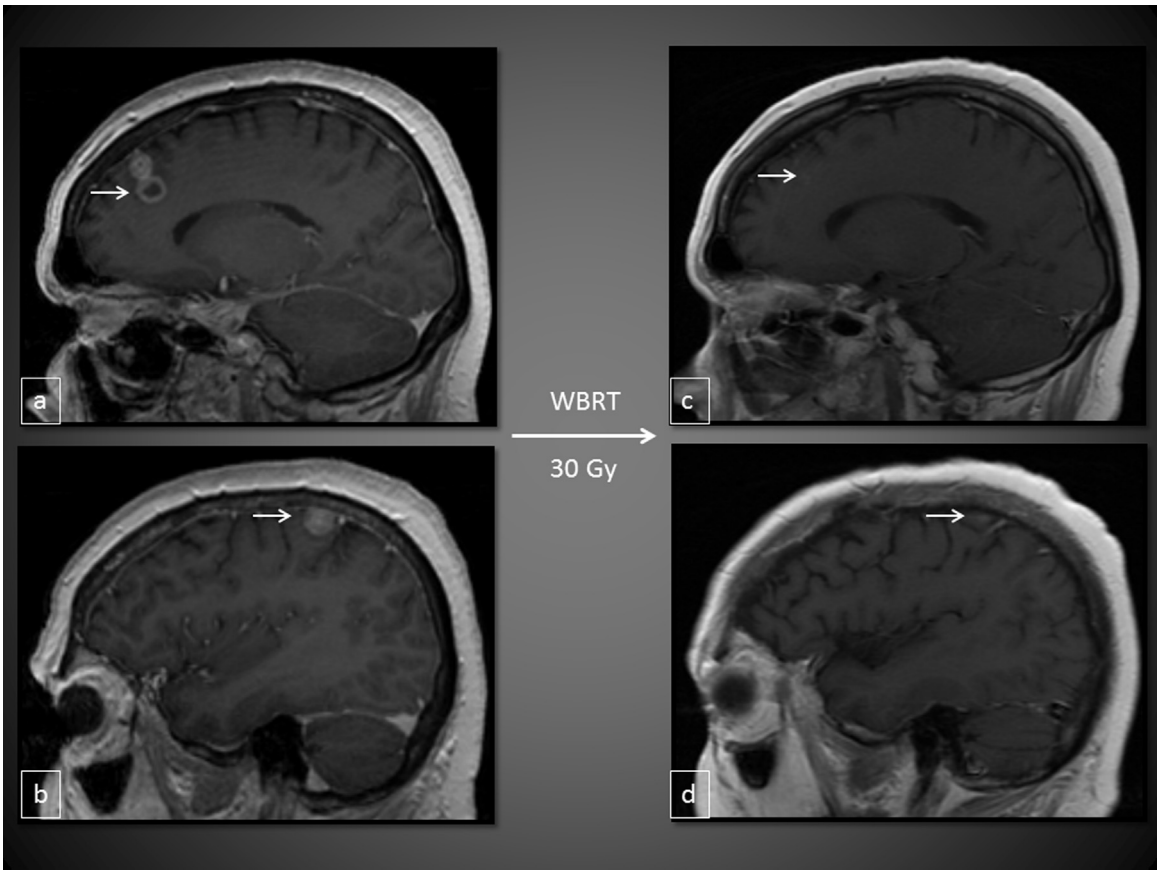

Fig. 1. 56 year old woman with ES-SCLC, metastatic to brain at the time of presentation. Sagittal T1-weighted contrast enhanced MRI of the brain shows (A) two enhancing left frontal lobe lesions and (B) a single left parietal metastasis. Following whole brain radiation with a total of 30 Gy in 10 fractions, only a faint blush is seen in the (C) frontal lobe and (D) parietal lobe, compatible with treated disease.

SCLC. Several early-phase clinical trials have suggested significant response rates to TMZ in SCLC, including a response rate of 38% amongst brain metastases within the CNS, yet medical oncologists have been slow to incorporate TMZ into their practice [5,6].

2. Case report

In July 2011, a 56 year old woman was diagnosed with ES-SCLC including intracranial, mediastinal lymph node and bone metastases (Fig. 1A and B). She initially received WBRT to 30 Gy (Gy) in 10 fractions in September 2011 (Fig. 1C and D). This was followed by platinum-etoposide, which was discontinued after three cycles due to intolerance. The patient achieved a radiographic complete response (CR) and remained with no evidence of disease (NED) until October 2012, when restaging magnetic resonance imaging (MRI) of the brain revealed 13 new brain metastases (Fig. 2A). Additional restaging imaging at this time revealed no extracranial evidence of disease.

In November 2012, she was initiated on TMZ 200 mg/m2 days 1–5 every 28 days. Restaging MRI brain after 8 weeks of systemic therapy revealed partial response (PR) (Fig. 2B) and a CR was noted by 24 weeks (Fig. 2C). She remained NED until restaging MRI brain in May 2014, when a single lesion was noted in the left frontal lobe, with a second lesion noted on repeat MRI brain one month later. She underwent SRS to 20 Gy to these lesions in June 2014 with temporary discontinuation of TMZ. She resumed TMZ after SRS and continued until December 2014 when restaging MRI brain showed additional intracranial metastases. She was again treated with SRS to 20 Gy directed at five lesions in January 2015 with brief discontinuation of TMZ. She then resumed TMZ, on which she has remained to date. Restaging scans have continued to show a CR over 4 years after initiating TMZ. The patient has tolerated TMZ at the above dose without issue, aside from grade 1 nausea and grade 1 fatigue.

3. Discussion

Previous data including a retrospective analysis from Ekeblad et al. have suggested efficacy for TMZ in advanced NE tumors, with response rates of 14%, while subsequent trials have suggested similar or better response rates specifically in SCLC [5–7]. Additional retrospective data from Kulke et al. have revealed that response to TMZ in NE tumors may correlate with those tumor types which express low levels of O(6)-methylguanine DNA methyltransferase (MGMT), with a significant difference between response rates in pancreatic NE tumors (51% MGMT-deficient, 34% response rate) compared to carcinoid tumors (0% MGMT-deficient, 2% response rate) [8]. This echoes similar findings regarding epigenetic silencing of MGMT expression as a biomarker of response to TMZ in gliomas [9,10]. Notably, a 2015 study by Miglio et al. found MGMT promoter methylation in 35.2% of SCLC samples [11].

Pietanza et al. published in 2012 the results of a Phase II study of TMZ 75 mg/m2 for 21 days every 28 days in relapsed SCLC [5]. Response rates were 23% in patients with platinum-sensitive disease and 13% in platinum-refractory patients. In this trial, response rates in brain metastases were 38%. Greater response rates were seen in cases with MGMT promoter methylation compared to those without (38% versus 7%). Based on its activity in this trial, TMZ was added in 2013 to the NCCN guidelines as an off-label option for relapsed SCLC [12].

Currently, combinations of TMZ with targeted agents are being investigated in SCLC. In particular, a Phase 2 randomized trial of TMZ and placebo vs TMZ and ABT-888 (veliparib) in patients with relapsed