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ORIGINAL ARTICLE

The efficacy of capecitabine and temozolomide against neuroendocrine carcinomas

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Abstract

Objective Neuroendocrine carcinomas (NECs) are resistant to currently available chemotherapy agents, and its therapeutic options are limited. Preclinical data have suggested synergy between capecitabine and temozolomide (CAPTEM). Therefore, we evaluated the efficacy and safety of CAPTEM in patients with metastatic NECs who have failed prior therapies.

Methods A retrospective review was conducted on seven patients with metastatic NECs for whom platinum-based chemotherapies and hepatic chemoembolization failed. Patients received capecitabine (1000 mg twice daily on days 1-14) and temozolomide (150–200 mg/m^2 once daily on days 10–14) every 28 days. Tumor assessments were performed every two cycles.

Results Among the seven patients treated, two achieved partial remission and four achieved stable disease. The total response rate was 29%, and the clinical benefit was 86%. Median progression-free survival was 10 (range: 8–14) months. The most common toxicities were grade 1 and 2 neutropenia, grade 1 fatigue, and grade 1 and 2 hand-foot syndrome. No grade 4 toxicities or treatment-related deaths were observed.

Conclusion Our study showed that the CAPTEM regimen is an effective and well-tolerated salvage option for NECs. Further prospective studies are warranted to evaluate optimal combinations of the CAPTEM regimen for NECs.

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Key words: temozolomide, capecitabine, neuroendocrine carcinomas

Neuroendocrine tumors (NETs) are characterized by their ability to secrete peptides, resulting in distinctive hormonal syndromes. They represent a heterogeneous group of tumors with varying biological and clinical behaviors based on their functionality and differentiation. NETs account for 1–2% of all malignancies, and recent epidemiological studies have revealed an increasing incidence of this type of cancer [1].

The World Health Organization classified NETs based on their differentiation and Ki-67 rate in order to assess their biological behavior and potential for a malignant phenotype. Neuroendocrine carcinomas (NECs) are classified into fast-growing, poorly differentiated tumors, with Ki-67 rate of > 20%. NECs are highly heterogeneous, including small cell type, large cell type, and mixed type, and are a part of well-differentiated NETs. Different types of NECs have varied sensitivity to drugs and prognosis. NECs with a Ki-67 rate of ≥ 55% are more responsive to platinum-based chemotherapies, and those with a Ki-67 rate between 20% and 55% are less responsive to platinum-based chemotherapies [2].

Temozolomide is an oral alkylating agent, with a mechanism of action similar to dacarbazine. The therapeutic benefit of temozolomide depends on its ability to methylate DNA, which most often occurs at the N-7 or O-6 positions of guanine residues. This methylation damages the DNA and triggers the death of tumor cells [3]. *In vitro* studies have suggested a synergistic activity of CAPTEM, an oral form of 5-FU [4]. The mechanism of synergism is uncertain. However, the data suggest that the synergy is dependent on the sequence of the two drugs. Temozolomide should be administered after the exposure of tumor cells to capecitabine. One possible explanation for this synergy is depletion of the DNA repair enzyme O^6-methylguanine DNA methyltransferase (MGMT) by capecitabine, thereby reinforcing the effect

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of temozolomide [5].

The efficacy of second-line treatment for NECs with capecitabine and temozolomide (CAPTEM) has rarely been explored. In this study, we present a retrospective analysis on its treatment efficacy and safety in seven patients with metastatic NECs who received CAPTEM as second-line treatment at the Department of Oncology, Inner Mongolia People's Hospital.

Materials and methods

Data of seven patients diagnosed with metastatic NECs were retrospectively reviewed between January 2009 and January 2014. Patients received capecitabine (Xeloda, Roche, 1000 mg twice daily on days 1–14) and temozolomide (Diqing, Tasly Diyi, 150 mg/m^2 once daily, and increased to 200 mg/m^2 in cycle 2 if well tolerated, on days 10–14) every 28 days. Clinical and pathologic characteristics are listed in Table 1.

Imaging was performed every two cycles, and serum tumor markers were measured every cycle. Response to treatment was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) parameters [6]. Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [7]. All patients were followed until progression or death before these data were analyzed.

Results

Based on the RECIST parameters, two patients achieved partial response and four achieved stable disease. The total response rate was 29%, and the clinical benefit (responders and stable disease) was 86%. Median progression-free survival was 10 (range: 8–14) months. The combination regimen was generally well tolerated. Grade 3 toxicities included grade 3 hand-foot syndrome and thrombocytopenia in one patient. The most common toxicities were grade 1 and 2 neutropenia, grade 1 fatigue, and grade 1 and 2 hand-foot syndrome. No patient discontinued treatment because of toxicities, and no grade 4 or treatment-related deaths were observed. One patient required dose reductions because of grade 3 hand-foot syndrome (Table 2).

Discussion

In general, patients with metastatic NECs have a poor prognosis and short-term survival. The standard option for advanced disease is chemotherapy. However, few treatment strategies are effective for patients who experience treatment failure.

This study aimed to evaluate the efficacy and tolerability of CAPTEM regimen as second-line treatment after a

Table 1 Characteristics of the seven patients enrolled

Characteristics	*n*
Age, median (range, years)	47 (26–68)
Male/female ratio	2:5
ECOG performance status	
0	1
1	3
2	3
KI-67 index (20%–55%)	7
Primary tumor	
Pancreas	4
Gastric	1
Colon	1
Rectum	1
Site of metastases	
Liver	3
Lymph nodes	4
Lung	1
No. of metastatic sites	
1	6
2	1
Elevated tumor markers	
(Chromogranin A, 5-HIAA)	4
Resection of primary tumor	4
Previous TAE/TACE	2

Note: TAE: transarterial embolization, TACE: transarterial chemoembolization

Table 2 Adverse events

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
	No.	No.	No.	No.
Hematologic				
Anemia	1	1		
Neutropenia	5	2		
Thrombocytopenia	2	1	1	
Nonhematologic				
Nausea	2	1		
Vomiting	1	1		
Anorexia	2	1		
Diarrhea	1			
Fatigue	6			
Elevated AST	1	1		
Elevated ALT	1	1		
Hand-foot syndrome	3	2	1	

platinum-based chemotherapy in patients with NECs. We have observed a response rate of 29% and a clinical benefit rate of 86% among patients with metastatic NECs treated with CAPTEM regimen. The median progression-free survival was 10 months. No grade 4 toxicities were associated with this regimen. Grade 3 events were also limited. The dosage of our CAPTEM regimen was well tolerated with a good safety profile. The high clinical benefit rate and low toxicity rate in our study appear to validate this treatment strategy.

Among the four patients with pancreatic neuroendocrine carcinomas (PECAs), one achieved partial remission and three obtained a stable disease status. The synergism of CAPTEM is not fully understood. Preliminary evidence revealed that PECAs express low levels of MGMT [8], which perhaps explains the high level of chemosensitivity to temozolomide. In the future, more experiments should be designed to investigate whether MGMT expression in metastatic NECs correlates with response to CAPTEM.

The nuclear antigen Ki-67 may be a prognostic indicator and a surrogate marker [9]. Previous analysis showed a significantly shorter median survival in patients with a Ki-67 rate of ≥ 50%. The study on temozolomide-based chemotherapy against NECs also found more responders among patients with a Ki-67 rate of < 60% than among those with a higher Ki-67 rate [10]. This suggests that there are biological differences in the tumor between those with high and low Ki-67 rates.

Although the number of cases in our study is small, it triggers interest for future studies. In order to establish a standard regimen for NECs, a randomized study comparing CAPTEM and platinum-based treatments should be considered. In addition, to optimize the result of the investigation, patients should be selected based on the appropriate Ki-67 rate (< 55%).

Conflicts of interest

The authors declare to have no conflicts of interest.

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