Safety and efficacy of combining capecitabine and temozolomide (CAPTEM) to treat advanced neuroendocrine neoplasms

A meta-analysis

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Abstract

Retrospective studies have suggested that capecitabine combined with temozolomide (CAPTEM) is effective for treating patients with advanced neuroendocrine neoplasms (NENs); however, the efficacy and safety of this regimen needs to be verified by high-quality evidence or results of randomized controlled trials.

We carried out a meta-analysis to evaluate the safety and effectiveness of a CAPTEM protocol for patients with advanced NENs. Systematic electronic literature searches were conducted using PubMed, EMBASE, and the Cochrane Library, and among meeting abstracts of the American Society of Clinical Oncology, European Society for Medical Oncology, European Neuroendocrine Tumor Society, and North American Neuroendocrine Tumor Society, up to June 30, 2017. We selected studies describing CAPTEM regimens for treating advanced NENs and reported on tumor response and/or toxicities according to clear World Health Organization (WHO) grading of patients. Three reviewers independently and repeatedly identified studies, extracted data, and assessed the quality of the literature. A single-proportion meta-analysis was applied to included articles.

Fifteen studies with a total of 384 individuals were included. Medium overall survival in most studies was more than 12 months, whereas medium progression-free survival was similar or slightly higher than that in studies using other treatment regimes. Disease control rate of CAPTEM administration for patients with NENs was 72.89% (95% confidence interval. 64.04–81.73%; 95% confidence interval. 82.4%; P < .01). WHO grade 3 to 4 toxicities, such as thrombocytopenia (3.36%), neutropenia (0.69%), lymphopenia (0.65%), anemia (0.50%), mucositis (0.57%), fatigue (0.54%), diarrhea (0.49%), nausea (0.39%), and transaminase elevation (0.13%) were reported in the trials included.

CAPTEM is effective and relatively safe for treating patients with advanced NENs.

Keywords: capecitabine, disease control rate, neuroendocrine neoplasms, temozolomide, toxicities, World Health Organization grade

1. Introduction

Neuroendocrine neoplasms (NENs) are a rare group of tumors whose incidence has been significantly increasing every year.1 NENs are highly heterogeneous tumors, and their classification criteria and prognoses vary according to their presence in different organs.2 One study of 35,618 patients reported that 20.60% of patients were found to already have distant metastases upon initial diagnosis.1 In another study, median survival was only 19 months for patients with metastatic disease, 33 months for G1/G2 patients, and 5 months for G3 patients.3 Comprehensive treatment should be applied in patients with advanced NENs. For patients with unresectable disease who are asymptomatic, and have a low tumor burden and stable disease, observation with marker assessment and abdominal/pelvic multiphasic computed tomography or magnetic resonance imaging scans every 3 to 12 months as clinically indicated should be considered until clinically significant disease progression occurs. For patients with symptomatic, severe tumor burden, or severe tumor progression, lanreotide or octreotide should be
administered. Several studies suggest that molecularly targeted therapies such as everolimus, sunitinib, or cytotoxic chemotherapy should be administered to patients with tumors that continue to progress. The alkylating agents streptozotocin and temozolomide appear to have the most antitumor activity in NENs, especially in pancreatic NENs. Many studies have suggested that capecitabine combined with temozolomide (CAPTEM) is effective in patients with advanced NENs, resulting in high objective response rates and considerably low toxicity; however, the efficacy and safety of this regimen needs to be verified by high-quality evidence or results of randomized controlled trials. Therefore, in this article, we have evaluated the safety and efficacy of temozolomide combined with CAPTEM in patients with advanced NENs in a single-proportion meta-analysis.

2. Methods

2.1. Selection criteria

The following criteria were used to identify eligible studies: studies describing temozolomide and capecitabine as a combination treatment for advanced NENs; studies reporting tumor response outcome measures and/or toxicities, and studies clearly reporting World Health Organization (WHO) grading of patients. The following exclusion criteria were applied: case reports, editorials, commentaries, meta-analyses, review articles, and animal studies; experimental studies, and non-English language articles.

2.2. Literature search

A literature search for articles was performed using 3 major electronic databases (PubMed, EMBASE, and the Cochrane Library). The terms were combined with the Cochrane MEDLINE filter for studies. The search strategy for MEDLINE is available in the published protocol CRD42017071033. The search terms were adapted for use with other bibliographic databases in combination with database-specific filters for controlled trials, where these were available. Articles written in English were included. Meeting abstracts, including those of the American Society of Clinical Oncology, European Society for Medical Oncology, European Neuroendocrine Tumor Society, and North American Neuroendocrine Tumor Society were also checked. The search strategy was as follows: (“temozolomide” OR “methazolastone” OR “M and B-39831” OR “NSC-362856” OR “Temodal” OR “TMZ-Bioshuttle” OR “CCRG-81045” OR “Temodar”) AND (“Capecitabine” OR “N(4)-pentyloxy carbonyl-5′-deoxy-5-fluorocytidine” OR “Xeloda”) AND (“Neuroendocrine Tumors” OR “Carcinoma, Neuroendocrine” OR “Carcinoid Tumor” OR “Neuroendocrine Tumor” OR “Tumor, Neuroendocrine” OR “Tumors, Neuroendocrine” OR “Carcinoid Tumor, Neuroendocrine Carcinoid, Neuroendocrine Carcinoma” OR “Neuroendocrine Carcinoid” OR “Goblet Cell” OR “Goblet Cell Carcinoid” OR “Argentaffinoma” OR “Argentaffinomas”). We retained any article that described the effect of CAPTEM in the treatment of advanced NENs. Review articles, opinion pieces, and articles published after June 2017 were excluded. All searched articles were reviewed by 3 authors, and disagreements were resolved via discussion.

2.3. Literature quality evaluation

We applied the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies, which accommodated the studies included in this meta-analysis. This methodology comprised 9 evaluation criteria, which included the following: research design (patients whose diagnoses were clearly defined, cohorts with >95% of patients having advanced NENs, and follow-up times of >1.5 years); comparability (records of patients’ ages and sexes, Eastern Cooperative Oncology Group performance status (ECOG ps), and tumor staging); and assessment of outcomes [median progression-free survival (mPFS), disease control rate (DCR), and rate of patients who had grade 3–4 toxicities].

2.4. Data extraction

Data were extracted from studies independently by 3 reviewers, and included the following: author; publication year; study design; patients’ ages and sexes, ECOG ps; primary tumor location; WHO histology grade; DCR; rate of all grade 3 to 4 toxicities; mPFS; and median overall survival (mOS).

2.5. Statistical methods

Meta-analysis was performed for the study’s main focus to calculate proportions and rates with corresponding 95% confidence intervals (CIs) using RGui software version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). Peters test and funnel plot were carried out to detect publication bias in the meta-analysis. To evaluate heterogeneity in the outcomes across the included studies, Higgins’ I² and Q test were used. A Q test P value of <.05 or an I² value of >50% indicated substantial heterogeneity. When there was little or no substantial heterogeneity between tests, we used a fixed effect model; otherwise, a random effect model was used. Once significant heterogeneity was established, meta-regression, sensitivity analysis, and subgroup analysis were applied to determine the source of the heterogeneity.

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

3. Results

3.1. A rapid systematic review and meta-analysis

This systematic review was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines. A total of 637 articles were identified in the 3 major electronic databases using the aforementioned search strategy. We excluded 257 duplicated articles, 1 system review, 26 review articles, 22 non-English language articles, and 17 case reports. A total of 300 articles with irrelevant content were excluded after review of the title and abstract. Four articles were excluded for duplicated data; 12 were excluded for not having clear histologic classifications, and another 3 were excluded for lacking clear descriptions of tumor response and toxicities. Finally, 15 articles composed of 384 participants (Fig. 1) were retained. Of the 15 studies, 1 was a single-arm phase II trial and 14 were retrospective studies; moreover, a majority of articles had a score of 7+ or more in the Wells way literature quality evaluation (Table 1). The general characteristics of the literature and the baseline data are reported in Table 2.

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Figure 1. Literature search flowchart.
Table 1

| Study, year | Literature quality evaluation. |
|-------------|---------------------------------|
| Abbasi, 2014 | Retrospective Capecitabine of 600 mg/m² bid on days 1–14; temozolomide of 150–200 mg/m² on days 10–14; 28-day cycle |
| Chaves, 2016 | Retrospective Capecitabine of 1500–2500 mg/m² bid on days 1–14; temozolomide of 150–200 mg/m² on days 10–14; 28-day cycle |
| Crespo, 2016 | Retrospective Capecitabine of 750–1000 mg/m² bid on days 1–14; temozolomide of 150–200 mg/m² on days 10–14; 28-day cycle |
| Fine, 2013 | Retrospective Capecitabine and temozolomide |
| Fine, 2014 | Retrospective Capecitabine of 600–1000 mg/m² bid on days 1–14; temozolomide of 150–200 mg/m² on days 10–14; 28-day cycle |
| Ganetsky, 2012 | Retrospective Capecitabine and temozolomide |
| Liu, 2017 | Retrospective Capecitabine of 600–750 mg/m² bid on days 1–14; temozolomide of 150–200 mg/m² on days 10–14; 28-day cycle |
| Lopez, 2013 | Retrospective Capecitabine of 1000 mg/m² bid on days 1–14; temozolomide of 150 mg/m² on days 10–14; 28-day cycle |
| Ramírez, 2016 | Retrospective Capecitabine of 750 mg/m² bid on days 1–14; temozolomide of 200 mg/m² on days 10–14; 28-day cycle |
| Saif, 2013 | Retrospective Capecitabine of 1000 mg/m² bid on days 1–14; temozolomide of 200 mg/m² on days 10–14; 28-day cycle |
| Spada, 2015 | Retrospective Capecitabine and temozolomide |
| Strosberg, 2011 | Retrospective Capecitabine of 750 mg/m² bid on days 1–14; temozolomide of 200 mg/m² on days 10–14; 28-day cycle |
| Tran, 2015 | Retrospective Capecitabine of 600 mg/m² bid on days 1–14; temozolomide of 150–200 mg/m² on days 10–14; 28-day cycle |
| Wein, 2011 | Retrospective Capecitabine of 750–1000 mg/m² bid on days 1–14; temozolomide of 150–200 mg/m² on days 10–14; bevacizumab 5 mg/kg on days 14 and 28; 28-day cycle |

1. Patients clear defined and >95% advanced NENs; 2. meet the inclusion criteria; 3. follow-up time long enough (>1.5 years); 4. patients’ age and sex; 5. Eastern Cooperative Oncology Group performance status (ECOG ps); 6. tumor staging; 7. disease control rate (DCR); 8. rate of grade 3/4 toxicities; 9. median progression-free survival (mPFS).
3.2. Patients’ characteristics

The number of patients from the included studies ranged from 6 to 65, and the average age of patients ranged from 47 to 66 years. Six trials reported ECOG ps, which ranged from 0 to 2. All patients had diagnosed NENs.

3.3. Treatment regimens

A CAPTEM regimen was administered in all studies until either disease progression or unacceptable toxicity levels were reached (Fig. 2). The differences in dosing of CAPTEM are shown in Table 2.

3.4. Progression-free survival and overall survival

mPFS was reported in 12 of the included studies, ranging from 3.4 to 18 months, as shown in Table 3. The mPFS ranged between 3.4 and 6 months in studies of patients with WHO-graded G3 NENs, 12 to 18 months in studies reporting patients with G1/G2 NENs, and 8.9 to 16.4 months in studies with mixed-grade WHO patients.

mOS was reported in 7 out of 15 studies and ranged from 8 to 83 months (Table 3).

3.5. Tumor response

All studies assessed tumor response using Response Evaluation Criteria in Solid Tumors. All the DCR was reported in all studies and ranged from 44.00% to 96.67%. The meta-analysis of DCR showed that the DCR of CAPTEM for patients with NENs was 72.89% (95% CI, 64.04%–81.73%; I² = 82.4%; P < .01) in a random effect model, and sensitivity analysis showed that no study directly affected the results of this meta-analysis (Fig. 3A, B). A single covariate meta-regression analysis showed that patients’ WHO grade (I²_res = 36.28%; P < .001) could account for the heterogeneity among the outcomes and, consequently, affect the results. According to subgroup analysis, DCR was 91.07% (95% CI, 85.19%–96.96%; I² = 45.4%; P = .10) in studies that reported patients with G1/G2 NENs, 65.83% (95% CI, 58.46%–73.20%; I² = 2.2%; P = .40) in studies that included multiple grades of NENs, and 56.91% (95% CI, 56.91%–64.96%; I² = 0%; P = .60) in studies that included patients with G3 NENs.

### Table 3

| Study, year | Patients | mOS (M) | mPFS (M) | DCR (n) | CR (n) | PR (n) | SD (n) | PD (n) | Ref |
|------------|----------|---------|----------|---------|--------|--------|--------|--------|-----|
| Abbasi, 2014 | 21 | N/A | 16.5 | 80.95%(17) | 0.00%(0) | 57.14%(12) | 23.81%(5) | 19.04%(4) | [16] |
| Chaves, 2016 | 10 | 48 | N/A | 50.00%(5) | 10.00%(1) | 10.00%(1) | 30.00%(3) | 20.00%(2) | [17] |
| Crespo, 2016 | 65 | 38.3 | 16.1 | 89.23%(58) | 3.10%(2) | 44.60%(29) | 41.50%(27) | 10.80%(7) | [18] |
| Crespo, 2016 | 25 | 8 | 4.4 | 44.00%(11) | 0.00%(0) | 4.00%(1) | 40.00%(10) | 0.00%(0) | [19] |
| Fine, 2013 | 18 | 8 | 4.4 | 77.78%(14) | 5.50%(1) | 3.10%(2) | 44.60%(29) | 41.50%(27) | [20] |
| Fine, 2014 | 28 | N/R | N/R | 96.43(27) | 10.71%(3) | 32.14%(9) | 41.50%(27) | 10.80%(7) | [21] |
| Ganetsky, 2012 | 20 | N/A | 16.4 | 65.00%(13) | 0.00%(0) | 30.00%(6) | 35.00%(5) | 35.00%(7) | [22] |
| Liu, 2017 | 14 | N/R | 8.9 | 42.86%(6) | 7.14%(1) | 7.14%(1) | 32.14%(9) | 41.50%(27) | [23] |
| Lopez, 2013 | 34 | N/A | 12 | 65.52%(19) | 0.00%(0) | 42.86%(13) | 32.40%(11) | 0.00%(0) | [24] |
| Ramires, 2016 | 29 | na | 12 | 70.59%(24) | 0.00%(0) | 42.86%(13) | 32.40%(11) | 0.00%(0) | [25] |
| Sall, 2013 | 7 | 12 | 71.43(5) | 0.00%(0) | 42.86%(13) | 32.40%(11) | 0.00%(0) | [26] |
| Spada, 2015 | 52 | N/A | N/A | 71.15%(27) | 0.00%(0) | 29.00%(15) | 43.00%(22) | 0.00%(0) | [27] |
| Stroeborg, 2011 | 30 | N/A | 18 | 96.43(27) | 0.00%(0) | 70.00%(21) | 26.67(8) | 3.33(1) | [28] |
| Tran, 2015 | 6 | N/A | 3.4 | 50.00%(2) | 0.00%(0) | 16.67%(1) | 33.33%(2) | 0.00%(0) | [29] |
| Welin, 2011 | 25 | 22 | 6 | 72.00%(18) | 0.00%(0) | 28.00%(7) | 40.00%(10) | 28.00%(7) | [30] |

**Note**: CR = complete response, DCR = disease control rate, G = grade, mOS = median overall survival, mPFS = median progression-free survival, N/A = not applicable, N/R = not reported, PR = partial response, SD = stable disease.
36.44%–77.39%; \( I^2 = 56.2\% \); \( P = .10 \) in G3 exclusive studies (Fig. 3C). All results shown in a funnel plot were symmetric, and the \( P \) value of the Peters test was .1074 (\( t = -1.7294, \text{df}=13, P = .107 \)), which suggests no significant publication bias (Fig. 3D). Details of different response subtypes in each study are reported in Table 3.

### 3.6. Toxicities

In the safety analysis, which included 13 studies, Higgins’ \( I^2 \) and \( Q \) test results indicated no heterogeneity in the meta-analysis for toxicities (Fig. 4, Table 4). The most frequently observed severe toxicities (grades 3–4) were blood and lymphatic system disorders: thrombocytopenia (3.36%; 95% CI, 1.16%–
5.55%), neutropenia (0.69%; 95% CI, 0–2.29%), lymphopenia (0.65%; 95% CI, 0–2.08%), and anemia (0.59%; 95% CI, 0–2.10%). Moreover, mucositis (0.57%; 95% CI, 0–2.02%), fatigue (0.54%; 95% CI, 0–1.93%), diarrhea (0.49%, 95% CI, 0–1.88%), and nausea (0.39%; 95% CI, 0–1.72%) were reported in the trials included. Only 1 in 336 patients had grade 3 transaminase elevation among all studies in this meta-analysis (Fig. 5).

### 4. Discussion

Recently, a number of randomized controlled trials have provided more treatment options for patients with advanced NENs.[3–6,29,30] However, due to the few number of known predictive factors for the treatment of advanced NENs, the management of these neoplasms has primarily relied on clinical and pathological factors, as well as each patient’s specific circumstances. It has been suggested that somatostatin analogs such as octreotide or lanreotide should be considered for patients with symptomatic, clinically significant tumor burdens or severe disease progression.[3,4] With regard to disease progression, administration of everolimus, sunitinib, or cytotoxic chemotherapy has been confirmed as optimal.[5,6,29,30] The order in which the drugs are administered should consider both efficacy and toxicity, and maintenance therapy should avoid the toxicity of long-term use of chemotherapy or molecule-targeted drugs.

According to Yao et al[5,30] for patients with advanced, low-grade, or intermediate-grade pancreatic neuroendocrine tumor (pNETs), the mPFS of the everolimus group was 11.0 months, which was significantly higher than the 4.6 months in the placebo group, whereas the mOS was 44.0 months in the everolimus group and 37.7 months in the placebo group. Similarly, a phase-3

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**Table 4**

| Study          | Patients | Thrombocytopenia | Neutropenia | Lymphopenia | Anemia | Mucositis | Fatigue | Diarrhea | Nausea | Transaminase elevation | Grade Ref |
|----------------|----------|------------------|-------------|-------------|--------|-----------|---------|----------|--------|------------------------|-----------|
| Abbasi, 2014   | 21       | 0                | 0           | 0           | 0      | 0         | 0       | 0        | 0      | 0                      | G1/2      |
| Chaves, 2016   | 10       | 0                | 0           | 0           | 0      | 0         | 0       | 0        | 0      | 0                      | G1/2      |
| Crespo, 2016   | 65       | 7                | 5           | 0           | 2      | 1         | 0       | 0        | 0      | 0                      | G1/2      |
| Fine, 2016     | 25       | 0                | 0           | 0           | 0      | 0         | 0       | 0        | 0      | 0                      | G1/2      |
| Fine, 2014     | 38       | 2                | 0           | 5           | 0      | 1         | 5       | 5        | 1      | 0                      | G1/2      |
| Ganetley, 2012 | 20       | 0                | 0           | 1           | 0      | 0         | 3       | 1        | 0      | 0                      | MX        |
| Liu, 2017      | 14       | 0                | 0           | 0           | 0      | 0         | 0       | 0        | 0      | 0                      | MX        |
| Lopez, 2013    | 34       | 3                | 3           | 3           | 0      | 0         | 0       | 0        | 0      | 0                      | MX        |
| Ramirez, 2016  | 29       | 3                | 3           | 3           | 3      | 0         | 0       | 2        | 1      | 0                      | MX        |
| Salt, 2013     | 7        | 1                | 0           | 0           | 0      | 0         | 1       | 0        | 0      | 0                      | G1/2      |
| Strosberg, 2011| 30       | 1                | 0           | 0           | 1      | 0         | 1       | 0        | 0      | 1                      | G1/2      |
| Welin, 2011    | 25       | 1                | 0           | 1           | 0      | 0         | 0       | 0        | 0      | 0                      | G3        |
| **Total**      | 336      | 20               | 8           | 10          | 3      | 2         | 10      | 8        | 3      | 1                      |            |

Proportion (95% CI) = 3.36% (1.16%, 5.55%), 0.69% (0.00%, 2.29%), 0.65% (0.00%, 2.08%), 0.59% (0.00%, 2.10%), 0.57% (0.00%, 2.02%), 0.54% (0.00%, 1.93%), 0.49% (0.00%, 1.88%), 0.39% (0.00%, 1.72%), 0.13% (0.00%, 1.42%)

CI = confidence interval, MIX = mixed-grade WHO patients.

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**Figure 5.** Rate of all reported adverse events after treatment with capecitabine and temozolomide (CAPTEM) for advanced neuroendocrine neoplasms (NENs). Trans. = transaminase. The vertical error bars represent the 95% confidence intervals for the rate of all reported adverse events from CAPTEM treatment in advanced neuroendocrine neoplasms (NENs).
trial conducted by Raymond et al.\[6\] showed that, for advanced NENs, the mPFS of the sunitinib group was 11.4 months as compared to that of the placebo group, 5.5 months. However, in another study of advanced pNETs, mPFS in the sunitinib group was 12.6 versus 5.8 months in the placebo group, and the mOS of the sunitinib group was 38.6 versus 29.1 months in the placebo group.\[29\] Caplin et al.\[3\] suggested that, for patients with ki-67 <10% with metastatic enteropancreatic neuroendocrine tumors treated with long-acting lanreotide and placebo, an mPFS for the lanreotide group was not reached versus the 18 months for the placebo group.

Although a number of treatment regimens have been associated with antitumor activity in these types of neoplasms, there has been no general consensus or guidance on the optimal cytotoxic chemotherapy regimen for patients with advanced NENs. One study revealed that capecitabine was safe and well tolerated by patients with advanced NENs and effective in patients with non-pNETs.\[31\] Meanwhile, another study suggested that temozolomide had an antitumor effect in advanced NENs when administered as a monotherapy, and its toxicity was acceptable.\[32\] Strosberg et al.\[10\] showed that the CAPTEM elicited a high and durable response rate in metastatic NENs when administered as a monotherapy, and its toxicity was acceptable.\[32\] These results suggest that CAPTEM regimens may prolong the survival of patients with advanced NENs and, therefore, deserve further attention.

All the included studies reported DCR, and this meta-analysis showed that DCR of a CAPTEM protocol for advanced NENs was greater than the DCRs reported in studies administering other agents or temozolomide monotherapy (Fig. 6).\[7\]–\[9,31,32\] Our results, as shown by the sensitivity analyses, indicate that no single study had a direct effect on the outcome. To explore the source of heterogeneity, a single covariate metaregression analysis was performed by restricted maximum likelihood methodology according to WHO grading, and the results indicate that WHO grading was associated with heterogeneity, even as high as 87.92%. Next, we divided the 15 included studies into 3 subgroups (G1/G2 group, G3 group, and mixed-grade group) by WHO grading. Subgroup analysis indicates that a CAPTEM regimen could be an effective treatment option for advanced low-intermediate grade NENs. Results also indicate low heterogeneity in that the $P$ value of the $Q$ test was >.05 in every group. Meanwhile, although all the studies used a CAPTEM protocol, the differences in drug dosing and cycles also led to heterogeneity (Table 1).

Similarly to other cytotoxic chemotherapies, the CAPTEM regimen is known to be associated with toxicities such as...
myelosuppression, hepatotoxicity, and gastrointestinal toxicities. Our meta-analysis showed that the more frequently observed severe toxicities were thrombocytopenia, neutropenia, lymphopenia, and anemia. The most severe chemotherapy side effects reported were high levels of lymphocytes and neutropenia, which leave patients susceptible to opportunistic infections. Moreover, these have been reported as the primary cause of discontinuation and/or reduction in dose in many studies and as resulting in routine prescription of antibiotics for patients receiving CAPTEM therapy.

A number of studies have shown that O6-methylguanine-DNA methyltransferase (MGMT) is a predictor of the efficacy of temozolomide in treating patients with advanced NENs. However, the mechanism behind the association between MGMT and temozolomide is unclear. A lack of MGMT deficiency in patients with NENs, as shown by immunohistochemistry, has been demonstrated in 24% to 51% of cases, whereas MGMT deficiency in cases of gastrointestinal NENs has not yet been reported. Further studies and clinical trials such as NCT01525082 are required to demonstrate the relationship between MGMT and temozolomide.

The results of this meta-analysis might have been affected by the small sample sizes and the low evidence level of the studies included. In addition, absence of a control group might have led to indirect comparisons with other cytotoxic chemotherapies.

In summary, the meta-analysis of available data suggests that CAPTEM is effective and relatively safe for patients with advanced NENs. However, the efficacy and safety of CAPTEM protocols should be further confirmed in future prospective studies.

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Author contributions
Yaoheng Lu created this idea and Li Lu designed the research. Ji Wang, Zhiheng Zhao, Wenhao LV, and Yaoheng Lu searched the literature using major electronic databases and then selected studies and data. Yaoheng Lu drafted this article. Weihua Fu and Weidong Li made important changes to this article. All authors have seen the manuscript and approved the submission.

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