Phase II Study of Oral Topotecan in Advanced Non-Small Cell Lung Cancer

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ABSTRACT

This study was designed to assess the activity of oral topotecan (TPT) in patients with advanced non-small cell lung cancer previously untreated with chemotherapy. Eligible patients had inoperable stage III or stage IV non-small cell lung cancer and were chemotherapy-naive. Other inclusion criteria were Eastern Cooperative Oncology Group performance status 0, 1, or 2, adequate bone marrow, and renal and hepatic function. Of 30 patients, 29 were assessable for response. Oral TPT was administered for 5 days every 21 days for up to six cycles unless disease progression or unacceptable toxicity occurred. Patients received a dose of 2.3 mg/m²/day for the first cycle. Dose modification for subsequent cycles was based on tolerability. Patients completed symptom questionnaires every 3 weeks. Pharmacokinetics were evaluated in all patients during cycle 1.

Three patients had radiological responses with a reduction in tumor size of 30–40%. No patients achieved complete or partial responses to treatment. Thirteen patients had a stable disease (43.3%), and the median survival was 39.9 weeks with a 1-year survival of 33.3%. At the time of analysis, 27 patients had died. Median time to progression was 12.3 weeks.

Treatment was well tolerated. A total of 125 cycles of treatment were completed. Twelve patients (40%) experienced grade III/IV neutropenia. Five patients (16.6%) had grade III/IV anemia. There were two episodes of grade III/IV thrombocytopenia. The main nonhematological toxicities consisted of grade III nausea (13%) and grade III vomiting (13%).

The most frequently reported disease-related symptoms at baseline were dyspnea, cough, and fatigue. There was a subsequent improvement in patient scores of dyspnea in 17% of patients, 31% showed improvement in cough, and 32% showed improvement in fatigue.

The mean area under the curve of TPT following 2.3 mg/m² p.o. was 51.6 ng.h/ml (%SD, 25%). The area under the curve of TPT on day 1 of the first cycle was correlated with the percentage fall in leukocytes.

Although oral TPT at the applied dose and schedule showed modest activity as a single agent, almost one-half of the patients had a stable disease, and median time to progression was 12.3 weeks. The overall median survival was a promising 39.9 weeks, and useful palliation of symptoms was seen.

INTRODUCTION

More than one-half of a million cases of lung cancer are diagnosed in the world annually. The majority of cases are NSCLC. Only a minority of these can be treated with curative resection. Meta-analyses have shown a survival benefit from cisplatin-based chemotherapy in advanced NSCLC (1–3). The quality of life and symptomatic benefit of chemotherapy with cisplatin-based regimens, however, were not addressed.

The development of new drugs has raised an expectation of improved activity and reduced toxicity. The camptothecin family of compounds has demonstrated activity in preclinical models and clinical studies of NSCLC (4). Camptothecin and its derivatives interfere with the function of topoisomerase I, forming a stable complex with the enzyme and DNA. In the S phase, advancing replication forks convert these complexes into cytotoxic double-stranded breaks (5).

TPT (9-dimethylaminomethyl-10-hydroxy-camptothecin) is a semisynthetic analogue of the plant alkaloid camptothecin. Initial Phase I studies of the i.v. formulation demonstrated the tolerability of the drug, with myelosuppression being the major toxicity (6). When given on a schedule daily for 5 days every 3 weeks, TPT was efficacious in relapsed ovarian cancer and small cell lung cancer (7, 8). Phase II studies of the i.v. formulation in non-small cell lung cancer have reported varying response rates of 0%, 4%, 15%, and 18.4% (9–12). The median survival of ~8 months in each of these studies was encouraging despite the low response rates. The feasibility of administering TPT p.o. has been tested (13). Such a formulation could have implications for patient convenience, schedule manipulation, and use in combined therapy protocols. Oral TPT was shown to have 32–44% bioavailability (14). Phase I studies demonstrated differing toxicities depending on the schedule. A protocol of twice daily for 21 days demonstrated an MTD of 0.5 mg/m².

The abbreviations used are: NSCLC, non-small cell lung cancer; TPT, topotecan; MTD, maximum-tolerated dose; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; SCC, squamous cell carcinoma; AUC, area under the curve.
with the DLT being diarrhea (15). The schedule of 5 days every 3 weeks showed an MTD of 2.3 mg/m²/day, with DLT being grade IV neutropenia (12). The i.v. MTD for the same schedule was 1.5 mg/m²/day (16).

In this study, we report the results of a Phase II study of oral TPT in chemotherapy-naive patients with advanced NSCLC. The primary efficacy variables assessed were response rate, duration of response, and time to disease progression. Secondary variables were survival, time to response, symptom changes, and pharmacokinetics.

PATIENTS AND METHODS

Patient Selection. Eligible patients were required to have histologically or cytologically documented stage III or IV NSCLC deemed not amenable to either surgery or radiotherapy with curative intent. No prior chemotherapy was permitted. All patients were required to have measurable disease, ECOG performance status of 0–2, 24-h creatinine clearance ≥ 60 ml/min, adequate bone marrow reserve (hemoglobin ≥ 9.0 g/dl, neutrophils ≥ 1500/mm³, platelets ≥ 100,000/mm³), and hepatic function (serum bilirubin ≤ 34 μmol/liter, transaminases and alkaline phosphatase ≤ two times the upper limit of normal) were required. Patients with known brain metastases were excluded from the study. Specific exclusion criteria were conditions affecting gastrointestinal motility or absorption, or patients on maintenance H₂ antagonists or proton pump inhibitors.

All patients gave informed, written consent, and the trial was approved by the local research ethics committee and conducted in accordance with good clinical practice obligations.

Treatment Schedule. Patients commenced treatment at a baseline TPT dose of 2.3 mg/m²/day p.o. daily for 5 days every 3 weeks. Patients received up to six cycles of treatment providing there was no unacceptable toxicity or evidence of disease progression.

Dose Modification. The treatment dose could be increased in subsequent cycles in steps of 0.4 mg/m², providing there was no grade III/IV toxicity. The maximum dose allowed was 3.1 mg/m²/day. The dose was reduced by 0.4 mg/m² if substantial toxicity was experienced with each cycle, e.g., grade IV thrombocytopenia or grade IV neutropenia associated with fever.

Pharmacokinetics. Blood samples for the determination of the pharmacokinetics were collected up to 12 h after dosing on day 1 of the first cycle. Samples were taken in all patients at the initial dose level and subsequently in four patients who received the maximum dose of 3.1 mg/m². Whole blood samples (3.0 ml) were collected into cold heparinized tubes before dosing at the nominal times of 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h. Samples were placed in ice and centrifuged within 10 min at 4°C at 1500 rpm. The sample was transferred to appropriately labeled polystyrene tubes and frozen on dry ice.

Plasma samples were stored at −30°C until analysis. Plasma samples were collected from patients at the Christie Hospital (Manchester, United Kingdom) and analyzed at the Netherlands Cancer Institute (Amsterdam, the Netherlands). Determination of plasma concentrations of total TPT was performed using high performance liquid chromatography with fluorescence detection (17). The lower limit of quantitation was 0.10 ng/ml based on a 100-μl aliquot of plasma. The average within run and between run precision was <1.5% for all quality control samples. The average accuracies were within 85% and 115%.

Pharmacokinetic analysis of the plasma concentration time point data for total TPT in each patients was analyzed separately by noncompartmental methods using WinNonlin Professional (version 1.5). Pharmacokinetic parameters determined for the total TPT concentration time data included maximum observed plasma concentration (Cₘₐₓ) and time to which Cₘₐₓ occurred (Tₘₐₓ). Area under the concentration time curve from zero to the time of the last quantifiable concentration (AUC 0-1) was determined using the linear trapezoidal rule for each incremental trapezoid up to the time of Cₘₐₓ and the log trapezoidal rule for each trapezoid thereafter. AUC extrapolated to infinity (AUC 0-∞) was calculated as the sum of AUC (0-1) and Cₘ₉/λ where Cₘ₉ is the predicted concentration at time t. The apparent terminal elimination rate constant (λ) was derived from the log-linear disposition phase of the concentration time curve using least squares regression analysis. With visual inspection of the data to determine the appropriate number of data points to include in the calculation of λ. The apparent terminal elimination half-life (T½) was calculated as ln2/λ.

Mean plasma concentrations were determined for each time point for each dose regimen and displayed graphically. Pharmacokinetic parameters were summarized descriptively (mean, median, SD, minimum, and maximum) for each regimen. Spearman rank correlations were calculated between AUC (t-∞) day 1 and the percentage decrease of WBCs.

Treatment Assessment. Patients were followed with weekly full blood examinations, and history, physical examination, urinalysis, and biochemistry at the commencement of each cycle. The objective response was evaluated according to WHO criteria with a more stringent definition of stable disease requiring a duration of at least 56 days. All claimed responses were subject to independent radiological review. Radiological assessment was performed at the baseline and following cycles 2, 4, and 6. Patients also completed a lung cancer-based symptom questionnaire before assessment on the day of treatment. Toxicities were graded according to National Cancer Institute common toxicity criteria.

Statistical Analysis. The primary aim of the study was the assessment of the response rate with oral TPT. The sample size of 30 patients allowed the true rate to be predicted with a SE of no more than 9.13%.

Time to progression was taken from the date of the first treatment to the date of the progression. Survival was calculated from the date of the first treatment to death, and a survival curve was formed using Kaplan-Meier estimation.

RESULTS

Patient Characteristics. Thirty patients entered the study at the Christie Hospital between September 1997 and April 1998. Patient characteristics are listed in Table 1. Two-thirds of the patients were male, and the median age was 61.5 years. All except 2 patients had performance status 1 or 2, and 18 patients (60%) had evidence of metastatic disease.

Chemotherapy Administration. Patients completed diaries to confirm tablet compliance. Twenty-eight patients com-
completed diaries for all cycles. Two patient diaries were incomplete for at least one cycle or treatment.

The thirty patients received a total of 125 cycles, 41 of these at the starting dose. Twenty-six patients (86.7%) had an increase in dose to 2.7 mg/m². A further 15 of the latter patients achieved either a complete or partial response to treatment, for at least one cycle or treatment. Twenty-six patients (86.7%) had an increase in dose to 2.7 mg/m². A further 15 of the latter patients achieved either a complete or partial response to treatment, for at least one cycle or treatment.

**Response and Survival.** There were no patients who achieved either a complete or partial response to treatment, although three patients had objective tumor shrinkage of <50%. Response to treatment is summarized in Table 2. Three patients were not assessable for tumor response. One patient was withdrawn after cycle 1 because of toxicity. Another patient was not assessable for tumor response due to the absence of measurable disease, and a further patient had stable disease that was not confirmed at 56 days. All patients with stable disease received six cycles of TPT. Patients who developed progressive disease received a median of three cycles. Median time to progression was 12.3 weeks. Median overall survival was 39.9 weeks (range, 4–59.1 weeks), and the 1-year survival was 33.3%.

Eighteen patients (60%) received palliative radiotherapy at the onset of symptomatic progression. Nine of 18 (50%) of the patients had disease stabilization, whereas the remainder progressed through radiotherapy. Ten patients (33%) received second-line cisplatin-based chemotherapy. One response was seen; four patients had stable disease, and the remainder progressed through treatment.

**Symptom Benefit.** Nine symptoms were evaluated on a four-point scale based on the Lung Cancer Symptom Score. A symptom improvement was defined as an amelioration of the symptom by one or more points, which were sustained for at least two treatment cycles, as described by von Pawel et al. (8). The results are summarized in Table 3. There was improvement in both respiratory symptoms and general symptoms, with dyspnea improving in 17% of patients, cough in 31%, chest pain in 20%, and hemoptysis in 33%.

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**Toxicities.** TPT was well tolerated at the administered schedule. The hematological toxicities experienced are listed in Table 4. Grade 3 or 4 neutropenia occurred in 22.6% of courses, and grade 3 or 4 leukopenia occurred in 16.9%. Grade 3 or 4 thrombocytopenia was uncommon, occurring in 1.6% of courses. Fever or infection of at least grade 2 was experienced by seven patients (23.3%), but only one patient experienced fever in the context of grade 4 neutropenia. Grade 3 or 4 anemia occurred in five patients. Sixteen patients received a blood transfusion at some stage during treatment, usually to ameliorate symptoms of fatigue or dyspnea. The mechanism of anemia was considered to be myelosuppression because none of the transfused patients demonstrated clinical signs of blood loss or had an abnormal blood film.

Nonhematological toxicities were generally mild, and subjective tolerability was excellent. No grade 4 nonhematological toxicity was experienced. Prophylactic antiemetics were not used routinely with grade 3 nausea and vomiting being experienced by only four patients (13.3%). Grade 1 or 2 diarrhea occurred in 11 patients. Six patients (20%) developed grade 2 alopecia, and 10 patients (30%) had grade 2 or 3 somnolence.

**Pharmacokinetics.** A total of 30 patients were enrolled and provided complete pharmacokinetic data on day 1 of cycle 1 after oral dosing of 2.3 mg/m². The pharmacokinetics following escalation to 3.1 mg/m² was studied in four patients who provided additional pharmacokinetic data on their first day of the new dose regimen.

After oral administration of 2.3 mg/m², total TPT plasma concentrations were quantifiable over the 12-h sampling interval. Peak plasma concentrations generally occurred within 2 h after dosing. The mean AUC (0–12h) was 51.6 ng.h/ml. Because the terminal phase was not well described in four patients, no extrapolation of the AUC could be performed. Therefore, AUC (0–∞) and T1/2 were not calculated for these patients. In the remaining 26 patients, mean AUC (0–∞) and T1/2 were 61.8 ng.h/ml and 3.96 h, respectively (See Table 5).

In the four patients escalated to 3.1 mg/m², total TPT concentrations were quantifiable over the 12-h sampling period. Peak plasma concentrations were 16.7 ng/ml, and AUC (0–12 h) and AUC (0–∞) were 76.6 and 85.0 ng.h/ml, respectively. The mean T1/2 following the 3.1-mg/m² dose was 3.56 h.

Spearman rank correlations were performed in the 26 patients who had an estimated AUC (0–∞). A statistically significant correlation between AUC (0–∞) and percentage fall in white cells (P = .002) was found, with a correlation coefficient of .575.

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**DISCUSSION**

This Phase II study reports only modest response activity of oral TPT at the applied dose and schedule. No partial or
The results of a neoadjuvant study also showed that improved survival (20–22). Conversely, an ECOG study comparing carboplatin to combination therapy showed superior response rates (23). The response rate of 8% (23).

Alopecia (grade 2) 5 16.7
Grade 3 1 3.3
Grade 4 1 3.3

Table 4  Toxicities (N = 30)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>5</td>
<td>16.7</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Grade 3</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>17</td>
<td>56.7</td>
</tr>
<tr>
<td>Grade 3</td>
<td>4</td>
<td>13.3</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Gastrointestinal, nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>8</td>
<td>26.7</td>
</tr>
<tr>
<td>Grade 3</td>
<td>4</td>
<td>13.3</td>
</tr>
<tr>
<td>Somnolence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Alopecia (grade 2)</td>
<td>5</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Forty-three percent of patients had stabilization of disease, with a median time to progression of 12.3 weeks. The median survival of 39.9 weeks and a 1-year survival of 33.3% appeared promising. Such results are in excess of typical survival figures in advanced lung cancer (18, 19). Although this may reflect a selection bias, it may also be possible that TPT has had an impact on the course of the disease. Similar survival results have been observed in Phase II studies of i.v. TPT in NSCLC (9–12). One of the latter studies had no responses and another study of infusional topotecan had a response rate of 4%.

Table 5  Pharmacokinetic parameters for total topotecan at 2.3 mg/m² orally

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>30</td>
<td>10.9 (5.63)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>30</td>
<td>2 (0.5–4.0)</td>
</tr>
<tr>
<td>$AUC$ (O–t) (ng.h/ml)</td>
<td>30</td>
<td>51.6 (25.5)</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>26</td>
<td>3.96 (0.573)</td>
</tr>
</tbody>
</table>

complete responses were seen, although three patients had an objective reduction in tumor size following treatment. The drug was convenient and well tolerated. Moreover, it alleviated symptoms in a proportion of patients.

Table 3  Symptomatic improvement

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of points with symptoms at baseline (%)</th>
<th>No. of affected points with 1+ point improvement</th>
<th>No. of affected points with 2+ point improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>29 (96)</td>
<td>5 (17)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>26 (87)</td>
<td>8 (31)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>20 (67)</td>
<td>4 (20)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>15 (50)</td>
<td>5 (33)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>26 (86)</td>
<td>8 (31)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>26 (87)</td>
<td>11 (43)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Hoarse voice</td>
<td>16 (54)</td>
<td>6 (38)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>28 (93)</td>
<td>9 (32)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Interference with daily activities</td>
<td>27 (90)</td>
<td>9 (33)</td>
<td></td>
</tr>
</tbody>
</table>

It has been suggested that topotecan may be more active against SCC than other NSCLC histological subtypes. This was hypothesized to explain the lack of response in the Lynch study where only 3 of 20 patients had SCC histology. Perez-Soler et al. (28) proceeded to the Phase II study of TPT treating only SCC of the lung, achieving a 24% RR. In our study where 10 of 30 patients had SCC histology, there were no objective responses in the subgroup, and indeed the three minor responses occurred in patients with non-SCC histology.

Could our results reflect a difference in the intensity of therapy between oral and IV TPT on a 5-day schedule? A bioavailability study demonstrated that the mean $AUC$ of oral TPT (57.9 h·ng/ml) was considerably lower than the mean $AUC$ of i.v. TPT at the MTD for the 5-day schedule (91.2 h·ng/ml; Ref. 29). Our results also yielded a similar mean $AUC$ for oral TPT. It is therefore possible that the lack of objective responses reflect a difference in intensity compared with i.v. TPT. Such a hypothesis would not be supported by the results of a
randomized study of small cell lung cancer patients; oral TPT given at the same dose and schedule as our study yielded similar response rates to IV TPT (30). Furthermore, no definite data from TPT studies has correlated cytotoxic activity with pharmacokinetic end points or dosage. Some in vitro data have suggested that time above a critical threshold is more important than actual AUC in the inhibition of topoisomerase I (31, 32).

It is unlikely that the lack of activity reflected an alteration in the ratio of the active lactone moiety:hydroxy acid form. Although this was not assessed in our study, the bioavailability study by Schellens et al. (14) reported no difference in this ratio between i.v. and oral administration of TPT.

It was evident that most of our patients could have tolerated a higher starting dose because 26 patients (87%) were dose-escalated after cycle 1 to 2.7 mg/m². A further 15 patients (50%) received the maximum protocol dose of 3.1 mg/m². The low dose intensity may have implications for achieving tumor cell kill, and conversely, an inadequate dose may theoretically promote the growth of resistant clones. Phase II studies with alternative schedules await examination in NSCLC. There is preclinical evidence that a prolonged exposure time to TPT may have greater efficacy (33). At a pharmacodynamic level, Hochster demonstrated that a 21-day infusion of TPT induced a progressive depletion of lymphocyte topoisomerase I levels until day 15, and this extended schedule may be worthy of assessment.

Oral TPT was well tolerated by patients, with a qualitative toxicity profile similar to the 5-day i.v. schedule, except that the incidence of grade 4 neutropenia was lower for oral topotecan (10%) compared to i.v. topotecan (47%; Ref. 9). Myelosuppression was the most prevalent toxicity, with 12 patients experiencing grade 3/4 neutropenia. Only one patient in our study experienced neutropenic fever. Mild anemia was common with over one-half of the patients requiring some transfusion support.

Mild to moderate nausea was seen in over one-third of patients but was easily controlled with antiemetic therapy. Diarrhea was uncommon and self-limiting. This is in contrast to the Phase I study of oral TPT using a schedule of twice daily for 21 days where diarrhea was the DLT. It occurred in the third week of drug administration, and the authors speculated that it may have resulted from an enhanced local effect of oral TPT on the gut mucosa with this schedule (15).

Interestingly, a correlation was found with total TPT AUC and the percentage fall in leukocytes. Similar findings were noted in three other i.v. TPT studies. Two of the studies observed that the total TPT AUC rather than the lactone AUC correlated better with neutrophil fall (34, 35). Reasons for this may have included intracellular conversion of the carboxylate to the lactone form or variability in the kinetics of the carboxylate form among patients treated with the same TPT dosage. A recent study comparing different schedules of oral TPT also found correlations between day 1 lactone AUC and myelosuppression. The authors concluded that the TPT plasma level rather than length of exposure to TPT was responsible for myelosuppression (36). These observations may have implications for combination therapy where additive myelosuppression may be lessened by a protracted schedule of oral TPT (37). The unpredictable and sometimes severe diarrhea seen with such schedules, however, may limit this application.

The minimal toxicity exhibited in cycle one implied that the initial 2.3-mg/m² dosage was conservative in a chemotherapy-naïve population. Eighty-seven percent of patients were dose-escalated, and only two of the remaining four patients had grade 3/4 myelosuppression. Accordingly, we would conclude that 2.7 mg/m² is a more appropriate commencement dose in untreated patients. The broad scatter of AUCs obtained in the pharmacokinetic analysis do not permit the development of a predictive model of individual dosing. Pharmacokinetic studies examining a much larger study population may, however, lead to a more refined dose.

Despite the modest activity demonstrated in this study, the oral formulation of TPT is convenient and has effects on stabilization that might translate to survival benefit in advanced lung cancer. Because oral TPT is well tolerated and provides symptom benefit, it may be useful in combination with platinum or taxane-based compounds. Some preclinical data suggests possible synergism between TPT and radiation (38), and topotecan and cisplatin (39). Combination Phase II studies are in progress.

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