Phase I Study of Irinotecan Combined with Carboplatin in Previously Untreated Solid Cancers

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ABSTRACT

Irinotecan (CPT-11) and carboplatin have broad antitumor activities. We conducted a Phase I study of CPT-11 combined with carboplatin in previously untreated solid cancers, especially advanced lung cancer. The aim of the study was to determine the maximum tolerated dose (MTD) and the dose-limiting toxicities in this regimen. In addition, we prospectively evaluated the Chatelut formula for predicting carboplatin clearance. Patients with advanced cancer were treated with CPT-11 (days 1, 8, and 15) and carboplatin (day 1) of a fixed-target area under the concentration-time curve (AUC) of 5 mg-min/ml. Carboplatin dose was determined by multiplying the AUC by the clearance predicted using the Chatelut formula. The CPT-11 dose was escalated from 40 mg/m² to the MTD by 10 mg/m². A total of 27 patients, 26 lung cancer patients and 1 colon cancer patient, were enrolled in this study. Dose-limiting leukopenia, thrombocytopenia, and diarrhea, including one treatment-related death, were observed at 60 mg/m² CPT-11, indicating that this level was the MTD. In 11 patients, the actual AUCs of carboplatin almost achieved the target AUC of 5. Fifteen (60%) of 25 evaluable patients showed an objective response, with an 85% response rate [11 of 13 patients (complete response, 31%; partial response, 54%)] in small cell lung cancers and a 36% response rate (4 of 11 patients) in non-small cell lung cancers. Neutropenia, thrombocytopenia, and diarrhea were the dose-limiting toxicities in this regimen. CPT-11 (50 mg/m²) under the carboplatin target AUC of 5 using the Chatelut formula was the recommended dose for further Phase II study, and this regimen seems to be active for small cell lung cancer.

INTRODUCTION

CPT-112 is a semisynthetic derivative of camptothecin and inhibits the function of DNA topoisomerase I by stabilizing a reversible enzyme-DNA cleavable complex (1, 2). This leads to single-strand DNA breaks and, ultimately, to the death of cancer cells (1, 2). Clinical studies of single-agent CPT-11 showed a broad spectrum of antitumor activity against lung, ovarian, cervical, and colorectal cancers (3). In addition, preclinical studies demonstrated synergism and non-cross-resistance between platinum agents and several topoisomerase I inhibitors, including CPT-11 (4–6). In fact, combination chemotherapy of CPT-11 with other agents such as cisplatin, etoposide, or 5-fluorouracil, has been investigated in various human cancers (3). Phase II studies of weekly CPT-11 with cisplatin yielded relatively high response rates of 84% and 52% in SCLC and NSCLC, respectively (7, 8). Thus, the combination of CPT-11 and platinum agents is probably an active regimen for solid cancer chemotherapy.

Carboplatin is an analogue of cisplatin with reduced nonhematological toxicities compared to cisplatin in experimental models (9). A number of Phase II and III studies have shown that carboplatin as well as cisplatin has a broad spectrum of antitumor activity and that the nonhematological toxicities of carboplatin were obviously less than those of cisplatin (10). On the other hand, pharmacokinetic studies of carboplatin have shown that thrombocytopenia, its major toxicity at maximal doses, depends strongly on the AUC of the ultrafilterable plasma concentration (11–13). Moreover, the actual carboplatin AUC appears to be correlated with therapeutic effectiveness in certain human cancers (13). Pharmacologically, AUC is closely related to the dose and CL of the drug. Based on these clinical findings, several formulas for predicting carboplatin CL in individual patients have been proposed to use carboplatin effectively and safely (13). Chatelut et al. (14) proposed a novel formula using biological markers that are easily obtained in the clinic.

Using the Chatelut formula, we conducted a Phase I study of a combination of weekly CPT-11 with a fixed-target carboplatin AUC of 5 mg-min/ml in previously untreated solid cancers. The main objectives of our study were to determine the MTD and the clinical toxicities encountered with this two-drug

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2 The abbreviations used are: CPT-11, irinotecan; MTD, maximum tolerated dose; DLT, dose-limiting toxicity; AUC, area under the concentration-time curve; CL, total body clearance; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; rhG-CSF, recombinant human granulocyte colony-stimulating factor; DI, dose intensity; PR, partial response; CR, complete response.

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Table 1  Dose-escalation and extension phase study
CPT-11 was administered on days 1, 8, and 15 of each cycle, and carboplatin was injected on day 1. CPT-11, mg/m²; AUC, mg · min/ml.

<table>
<thead>
<tr>
<th>Dose level</th>
<th>No. of patients</th>
<th>CPT-11 (day 1, 8, and 15)</th>
<th>Carboplatin target AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>3 (3)</td>
<td>50</td>
<td>5</td>
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<td>3</td>
<td>6 (7)</td>
<td>60</td>
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<tr>
<td>4</td>
<td>5</td>
<td>70</td>
<td>5</td>
</tr>
</tbody>
</table>

*The number in parentheses represent the number of patients enrolled in the extension phase study.

regimen. In addition, we prospectively evaluated the Chatelut formula with this regimen.

**PATIENTS AND METHODS**

**Patients.** The study protocol was approved by the Ethical Committee of Nagasaki University School of Medicine. Eligibility criteria for patients in this study included the following: (a) a histologically confirmed diagnosis of malignancy; (b) advanced-stage cancer without prior chemotherapy or radiotherapy; (c) no pleural or ascitic fluid; (d) age ≥ 75 years; (e) ECOG performance status = 2; (f) life expectancy of >12 weeks; (g) adequate bone marrow function (leukocyte count ≥ 4,000/µl, platelet count ≥ 100,000/µl, and hemoglobin level ≥ 9 g/dl); (h) serum bilirubin level ≤ 1.5 mg/dl; (i) alanine aminotransferase and aspartate aminotransferase levels ≤ 2 times the normal upper limit; (j) serum creatinine level ≤ 1.5 mg/dl; (k) no medical problems severe enough to prevent compliance with the protocol; and (l) provision of written informed consent.

**Treatment, Dose Escalation, and Extension Phase Study.** Under a fixed-target AUC of 5 mg·min/ml for carboplatin on day 1, the starting dose of CPT-11 was 40 mg/m² injected i.v. on days 1, 8, and 15. The dose of CPT-11 was increased by 10 mg/m² as shown in Table 1. The carboplatin dose was determined by multiplying the target AUC of 5 by carboplatin CL, which was predicted by the Chatelut formula using Jaffe method for serum creatinine measurement (14). Carboplatin was administered during a 60-min i.v. infusion with 250 ml of 5% dextrose, followed by 500 ml of normal saline as a 2-h infusion. This was followed by a 90-min i.v. infusion of CPT-11 in 250 ml of 5% dextrose. CPT-11 on day 8 or 15 in each cycle was cancelled when the patient had a leukocyte count < 3,000/µl, platelet count < 50,000/µl, or experienced diarrhea on each day. rhG-CSF was injected s.c. when the leukocyte or neutrophil count became <2,000/µl or <1,000/µl, respectively, and was discontinued when the count recovered to >10,000/µl or >5,000/µl, respectively. During rhG-CSF therapy, CPT-11 was never administered. The use of rhG-CSF is approved for this purpose in Japan. The next cycle at each level commenced after leukocyte and platelet counts reached at least 3,000/µl and 100,000/µl, respectively. In patients showing a response, this chemotherapy was repeated every 4 weeks.

The dose escalation was evaluated in the first cycle of each dose level, where toxicities were assessed according to the common toxicity criteria of the WHO (15). In the present study, DLT was defined as grade 4 leukopenia or neutropenia lasting 4 days or more, grade 4 thrombocytopenia, and grade 3 or worse nonhematological toxicity, with the exception of nausea and vomiting. In addition, DLT was also defined when CPT-11 on both day 8 and day 15 of each cycle was cancelled. For the dose escalation, three patients were enrolled at each dose level, and the dose was escalated to the next level when none of the patients experienced DLT. When two or more patients experienced DLT, the dose level was defined as the MTD. When one of three patients experienced DLT, an additional three patients were treated at the same level. When none of the additional patients experienced DLT, the dose was escalated to the next level. When one or more of the additional patients experienced DLT, the dose level was also defined as the MTD. The recommended dose of this regimen for Phase II study was defined as the previous level of MTD.

Additional patients were enrolled into the extension phase study to evaluate toxicities and safety at the recommended dose level defined above more accurately.

**Patient Evaluation and Response Assessment.** Tumor staging was based on a thorough medical history and physical examination, chest radiography, bone scintigraphy, computed tomography of the chest and abdomen, computed tomography or magnetic resonance imaging of the head, and endoscopy. The stage of malignancy was determined according to the tumor-node-metastasis (TNM) system (16). Before the first cycle, a blood cell count, urinalysis, and biochemistry tests for the assessment of renal and hepatic function and electrolytes were performed. These monitoring tests were repeated during treatment, whereas other investigations were repeated as necessary to evaluate marker lesions. After the completion of treatment, disease was assessed, and tumors were restaged.

The eligibility, assessability, and response of each patient were determined by extramural reviewers. Tumor response was classified according to the criteria of the WHO (15). A CR represented the disappearance of any evidence of tumors for at least 4 weeks. A PR was defined as a 50% or more reduction in the sum of the product of the greatest perpendicular diameter of all lesions for at least 4 weeks. No change was defined as a <50% reduction or ≤25% increase in the products of the greatest perpendicular diameters of all lesions, without any evidence of new lesions. Progressive disease was defined as an increase of >25% or the appearance of new lesions.

**Pharmacokinetics.** For the pharmacokinetic study of carboplatin, heparinized blood samples (2 ml) were obtained from the opposite arm of each patient in the first cycle at the following time points: (a) before the carboplatin infusion; (b) at the end of the infusion; (c) 15 and 30 min after the infusion; and (d) 1, 2, 4, 8, 12, and 24 h after the infusion. Each sample was immediately centrifuged at 1000 × g for 10 min, and the plasma was transferred to Amicon Centrifree (Amicon, Inc., Beverly, MA), followed by centrifugation with a fixed-angle rotor at 2000 × g for 25 min. The ultrafiltrates of plasma were stored at −20°C until the measurement of plasma-free platinum levels using flameless atomic absorption spectrophotometry (17).

The plasma-free platinum AUC (mg·min/ml) of carboplatin was calculated by the trapezoidal rule. The plasma carboplatin concentration at time 0 was considered as 0, and no correction during the period from the final time point to infinity was used. The rate constant (λz) was estimated by log-linear regression
analysis of the second phases of the postinfusion plasma concentration-time curves. The half-life ($t_{1/2}$) was calculated by the equation $t_{1/2}(\beta) = 0.693/\lambda_2$, and the volume at steady state ($V_{ss}$) was calculated by multiplying the dose by $t_{1/2}/0.693$ and AUC. The actual CL was calculated by dividing the actual dose by the actual AUC.

RESULTS

A total of 27 patients were enrolled in this trial between September 1995 and February 1998, and all received chemotherapy. Seventeen and 10 patients were enrolled in the dose escalation study and the extension phase study, respectively. The patient characteristics are shown in Table 2. Twenty-two patients (81%) had an ECOG performance status of 0–1, and all patients, except one patient with colon cancer, had lung cancer. The patient with colon cancer had multiple metastases in the liver and lungs. Lung cancers consisted of 14 SCLCs and 12 NSCLCs. All SCLCs were extensive-stage disease, and NSCLCs included one stage IIIA, three stage IIIB, and eight stage IV cancers. Unexpectedly, 13 SCLCs were enrolled in dose levels 3 and 4, and the remaining SCLC was enrolled in dose level 2.

A total of 63 cycles of this regimen were administered through four dose levels, and all were assessable for toxicity. One cycle was administered to eight patients (30%), two cycles were administered to eight patients (30%), three cycles were administered to five patients (18%), and four cycles were administered to six patients (22%); the median number of cycles administered was two. Nine of 18 patients at levels 3 and 4 and 2 of 9 patients at levels 1 and 2 received three cycles or more. As mentioned above, most patients with SCLC chemotherapy-sensitive tumors were enrolled in dose levels 3 and 4, whereas eight of nine patients enrolled at dose levels 1 and 2 had relatively resistant NSCLC and colon cancer.

Recommended Dose Level

None of the three patients at level 1 or 2 experienced DLTs. At level 3, one of three patients experienced DLTs (neutropenia and thrombocytopenia); therefore, an additional three patients were enrolled. None of the additional patients at level 3 experienced DLTs; thus, this study progressed to level 4. At level 4, one of three original patients experienced DLT (thrombocytopenia), and the second patient of the additional patients experienced DLT (neutropenia). At that time, level 4 was defined as the MTD, and level 3 was the recommended dose. However, as mentioned below, the MTD and the recommended dose level were changed in the next extension phase study.

Extension Phase Study

The study was extended to enroll additional patients at the dose level recommended above, level 3. Unexpectedly, seven patients were enrolled at almost same time. One of the seven patients concomitantly experienced dose-limiting thrombocytopenia, neutropenia, and diarrhea, had a high fever with abdominal pain and bloody stools, and ultimately died of renal failure on day 21 of the first cycle. This was considered to be a treatment-related death. In summary, five of the additional seven patients at level 3 experienced DLTs including one treatment-related death, and we considered level 3 as the MTD. Therefore, an additional three patients were enrolled into level 2, and none experienced DLTs. Finally, we concluded that level 2 was the recommended dose in this regimen.

Toxicity

Hematological Toxicity. Leukopenia and thrombocytopenia were the principal toxicities, as shown in Table 3. Nine (33%) of 27 patients experienced grade 4 hematological toxicities, and eight patients (30%) experienced hematological DLTs at level 3 and 4, including one treatment-related death. At dose levels 1 and 2, no patients experienced hematological DLTs in all treatment cycles, although only one patient at level 2 experienced grade 4 neutropenia lasting 2 days. At dose levels 3 and 4, dose-limiting grade 4 neutropenia and/or thrombocytopenia occurred in 8 of 18 patients in the first cycle, and 2 patients at dose level 3 required platelet transfusion. Anemia requiring blood transfusion was not observed in all treatment cycles at each level.

Nonhematological Toxicity. Gastrointestinal toxicities were prominent, such as nausea/vomiting, loss of appetite, diarrhea, and liver dysfunction (Table 3). Eighteen patients (67%) had diarrhea in the first cycle, and three patients (11%) at dose level 3 had grade 3 or worse diarrhea. Diarrhea of grade 3 or more occurred on day 13 (median; range, 10–18 days) and improved during days 14–21. Except for one treatment-related death, diarrhea was well controlled with loperamide (2–6 mg/day), although our doses of loperamide were lower than those used in other countries. No patients had grade 3 nausea/vomiting, and six patients (22%) showed liver dysfunction with a transient increase in serum transaminases. Other toxicities included transient dermatitis in two patients (7%) that appeared on both the hands and abdomen on day 6.

DI of CPT-11

Details of CPT-11 delivery and the DI at each level are shown in Table 4. During a total of 63 cycles, 49 skips on day...
8 or 15 were observed, and 28 (57%) skips occurred at the second cycle or later. The 49 skips included 13 skips on day 8 and 36 skips on day 15, and no skips on both day 8 and day 15 of each cycle were observed. The main reasons for skips on day 8 were leukopenia or diarrhea, and the main reasons for skips on day 15 were leukopenia, thrombocytopenia, and/or diarrhea.

The DI of the first cycle increased as the dose was increased. Compared to each DI of the first cycle, DIs of all cycles increased at dose levels 1 and 2 and decreased at levels 3 and 4. Consequently, the ratio of the actual DI:planned DI of all cycles decreased as the dose increased, and the DI of all cycles at level 2 exceeded that at dose level 3. The delay for the next cycle was not observed, and 43 skips on day 8 or day 15 were observed at dose levels 3 and 4. Therefore, the low DI in all cycles of the latter two levels was due to these skips, rather than to delays of the next cycle.

### Pharmacokinetics of Carboplatin

Pharmacokinetic analysis of carboplatin was performed in 11 patients (three patients at dose level 1, three patients at dose level 2, and five patients at dose level 3). The actual carboplatin dose using the Chatelut formula ranged from 408 mg/body (255 mg/m²) to 900 mg/body (547 mg/m²) in 11 patients, so the maximum difference in the dose was 2.21 times (measured in mg/body; 2.15 times measured in mg/m²). The plasma concentration-time curve and detailed pharmacokinetic parameters are shown in Fig. 1 and Table 5, respectively. The plasma concentration reached a maximum at the end of the infusion, and the mean values of peak plasma concentration, AUC, and $t_{1/2}$ are shown in Table 5. There were no significant differences in AUCs among the three dose levels, and the actual AUC was slightly lower than the target AUC of 5, a nonsignificant difference. The CL predicted by the Chatelut formula and the actual CL were 117 ± 34.9 ml/min (range, 81.6–180 ml/min) and 130 ± 44.4 ml/min (range, 80.0–229 ml/min), respectively, and a good correlation between these values was observed as shown in Fig. 2 ($r = 0.990; P < 0.0001$ by Pearson correlation).

**Response**

Twenty-five of 27 patients were assessable for response. An objective response was observed in patients with lung cancer, who an overall response rate of 60% (15 of 25 patients). In detail, 11 of 13 evaluable SCLCs (85%; 95% confidence interval, 55–98%) had a response (CR, 31%; PR, 54%), and 4 of 11 evaluable NSCLCs (36%; 95% confidence interval, 11–69%)...
volume at steady state (liter/m²).

concentration (g/ml); AUC, mg

cently, Okamoto et al. (18) also reported the results of a Phase I trial of CPT-11 and carboplatin with continuous use of prophylactic rhG-CSF for NSCLC. They recommended a CPT-11 dose of 60 mg/m² and a carboplatin AUC of 5 using the Chatelut formula for carboplatin CL. In their study, the DLT at the carboplatin target AUC of 6 was thrombocytopenia, where the actual AUCs in five patients almost reached the target AUC of 6. Jodrell et al. (19) reported an almost linear correlation between carboplatin AUCs of 5–10 and thrombocytopenia or leukopenia of grade 3 or worse in patients receiving carboplatin monotherapy. Thus, a carboplatin target AUC of 5 is thought to be appropriate in combination with CPT-11, although a target AUCs of 5–7 has been used in combination with other agents (13).

We determined the carboplatin dose in each patient by using the Chatelut formula for predicting carboplatin CL. This formula, which using parameters obtained easily in the clinic, is very convenient, and the parameters include gender, age, body weight, and serum creatinine level (14). In fact, the predicted carboplatin CLs in our 11 patients correlated well with the actual CLs (r = 0.990), and the actual AUCs almost achieved the target AUC of 5. This indicates that the Chatelut formula is probably a reliable prediction method to use in combination chemotherapy with CPT-11. In combination chemotherapy, patients with a high body weight, younger age, or good renal function can tolerate a substantially higher dose than the conventional carboplatin dose of 300 or 400 mg/m² that would otherwise seem to be an overdose in patients with greater age or poor renal function. The carboplatin doses ranged from 222 mg/m² (340 mg/body) to 547 mg/m² (900 mg/body) in all patients of the present study, where the maximum difference in dose was 2.46 (2.65) times. To date, several methods have been proposed for predicting carboplatin CL (13) and subsequently used to determine the AUC-based carboplatin dose. The Calvert formula (11) individualized CL by measuring the glomerular filtration rate using chromium 51-edathamil (51Cr-EDTA) administration; however, it is inconvenient for routine use. Although substitution of 24-h creatinine clearance for glomerular filtration rate is usually used to avoid this problem, the 24-h creatinine clearance is often widely dispersed because of incomplete 24-h urine collection (13). To provide more reliability to creatinine clearance, the Cockcroft-Gault formula (20) for predicting creatinine clearance is often used in clinical trials (13). In fact, in a Phase II study of paclitaxel and carboplatin using this formula, the actual median AUC of 4 was much lower than the target AUC of 5.21 (21). Van Warmerdam et al. (22) retrospectively evaluated the Chatelut and Calvert formulas using 24-h creatinine clearance and the Cockcroft-Gault calculation in patients receiving carboplatin and ifosfamide. They reported that the precision was similar in all methods. In this regard, additional prospective studies using a large number of patients and various combination regimens with carboplatin are necessary.

Earlier Phase I studies of CPT-11 and platinum agents with a schedule similar to the present study recommended 60 mg/m² CPT-11 (3, 18). CPT-11 (70 mg/m²) in these trials induced severe diarrhea as a DLT, but this was not observed at doses of 60 mg/m² or less. Considered together with the present results, the recommended 50 or 60 mg/m² CPT-11 seems to be appropriate in combination with a platinum agent. However, our

DISCUSSION

The present Phase I trial of CPT-11 (days 1, 8, and 15) and carboplatin (day 1) showed that the recommended CPT-11 dose was 50 mg/m²/dose under a carboplatin target AUC of 5 using the Chatelut formula for carboplatin CL. As expected, the main DLTs in the present study were thrombocytopenia, leukopenia, neutropenia, and diarrhea. Recently, Okamoto et al. (18) also reported the results of a Phase I trial of CPT-11 and carboplatin with continuous use of prophylactic rhG-CSF for NSCLC. They recommended a CPT-11 dose of 60 mg/m² and a carboplatin AUC of 5 using the Calvert formula for carboplatin CL. In their study, the DLT at the carboplatin target AUC of 6 was thrombocytopenia, where the actual AUCs in five patients almost reached the target AUC of 6. Jodrell et al. (19) reported an almost linear correlation between carboplatin AUCs of 5–10 and thrombocytopenia or leukopenia of grade 3 or worse in patients receiving carboplatin monotherapy. Thus, a carboplatin target AUC of 5 is thought to be appropriate in combination with CPT-11, although a target AUCs of 5–7 has been used in combination with other agents (13).

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patients at 60 mg/m² CPT-11 experienced DLTs of leukoneutropenia, thrombocytopenia, and diarrhea, including one treatment-related death. Similarly, in two Phase II trials of 60 mg/m² CPT-11 and cisplatin, grade 3 or worse leukopenia, diarrhea, and anemia were observed in approximately 45%, 20%, and 35% of approximately 70 patients, respectively, despite rhG-CSF support (7, 8). In addition, two treatment-related deaths due to these toxicities were observed in each trial (7, 8). These results indicate that 50 mg/m² CPT-11 rather than 60 mg/m² CPT-11 may be preferentially recommended in combination with a platinum agent, as shown in the present study. In fact, the DI at the 50 mg/m² dose level was not significantly decreased in both the first cycle and all cycles compared to the DI at 60 mg/m² CPT-11.

Interestingly, our results showed an 85% (CR, 31%) response rate in SCLC, which was comparable or superior to that seen in earlier trials of CPT-11 and cisplatin (7), cisplatin and etoposide (23), and vinorelbine and carboplatin (24). Unfortunately, a previous Phase I trial of CPT-11 and carboplatin could not evaluate response in SCLC because it was designed for NSCLC only, including previously treated cases of NSCLC (18). The present results indicate that our regimen may be a new effective regimen for SCLC. Recently, CPT-11 has been recognized as an active agent for SCLC, based on a modest response rate for relapsed SCLC and a high response rate for naïve limited- and extensive-stage SCLC (3, 7, 25). In addition, a high response rate in a Phase II trial in combination with cisplatin also yielded improved survival, especially in cases with extensive-stage SCLC (7). Although most SCLCs in the present study were treated at dose levels 3 and 4, the DI of CPT-11 in all cycles was almost similar to that of our recommended dose level 2. These findings indicate that our regimen is not inferior or equal to a regimen of CPT-11 and cisplatin for SCLC, although the number of patients in our study was too small to allow adequate evaluation of the response. Currently, we are conducting a Phase II trial of this regimen in extensive-stage SCLC.

In conclusion, we conducted a Phase I trial with CPT-11 (days 1, 8, and 15) and carboplatin (day 1), using the Chatelut formula for predicting carboplatin CL. The recommended CPT-11 dose was 50 mg/m² under a carboplatin target AUC of 5, and this combination chemotherapy seems to be an active regimen for SCLC. This regimen warrants additional Phase II studies, especially for SCLC.

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