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Phase II Study of a 3-Day Schedule with Topotecan and Cisplatin in Patients with Previously Untreated Small Cell Lung Cancer and Extensive Disease

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Introduction: Treatment with a topoisomerase I inhibitor in combination with a platinum results in superior or equal survival compared with etoposide-based treatment in extensive disease small cell lung cancer (SCLC). Five-day topotecan is inconvenient and therefore shorter schedules of topotecan and cisplatin are needed. The aim of this phase II study was to establish the response rate and response duration in chemo-naive patients with SCLC receiving a 3-day topotecan and cisplatin schedule.

Methods: Simons optimal two-stage design was used. Patients with previously untreated extensive disease SCLC, adequate organ functions and performance status less than 3 were eligible. Topotecan (2.0 mg/m^2, intravenously) was administered on days 1 to 3 with cisplatin (50 mg/m^2, intravenously) on day 3 every 3 weeks for a total of six cycles.

Results: Forty-three patients received 219 cycles of chemotherapy. Median age was 59 (range 44–74), 79% had performance status 0 or 1. Thirty-one patients completed all six cycles. Grade 3/4 anemia, neutrocytopenia, and thrombocytopenia were recorded in 9.5%, 66.7%, and 21.4% of patients, respectively. Fourteen percent of patients experienced neutropenic fever. No episodes of fatal sepsis occurred. Non-hematologic toxicity was mild and manageable. Overall and complete response rates were 72.1% and 9.3%, respectively. The median overall survival and response duration were 10.3 months (95% confidence interval: 8.6–12.0) and 7.0 months (95% confidence interval: 6.3–7.7), respectively.

Conclusion: Three-day topotecan with cisplatin on day 3 is active and safe in extensive disease SCLC. An ongoing phase III randomized trial compares this combination to standard treatment.

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The progress in the treatment of extensive disease small cell lung cancer (SCLC) has been at a standstill during the last 3 decades. There is an urgent need for new active agents in this disease entity. The topoisomerase I inhibitor topotecan is active as both first and second line therapy.[1–3] The combination with cisplatin has shown synergistic effects in preclinical models.[4] However, an unacceptable high frequency of toxic deaths was associated with the administration of cisplatin on day 1 in combination with 5-day topotecan.[5] As a consequence the reverse sequence with cisplatin on day 5 has been developed.[6,7] In this report, we have modified the 5-day schedule to a 3-day schedule to increase patient convenience. The primary end point of the study was to estimate response rate and response duration in chemo-naive extensive disease SCLC patients receiving a 3-day topotecan schedule with cisplatin on day 3. Secondary end points included toxicity and overall survival.

PATIENTS AND METHODS

Eligibility Criteria

Patients with histologically or cytologically confirmed extensive disease SCLC of the lung, including mixed histology, who had received no prior radio- or chemotherapy were eligible. Extensive disease was defined as disease beyond one hemithorax or with the presence of ipsilateral pleural effusion containing tumor cells. If the pathologic diagnosis was obtained from a metastatic lesion, the presence of either pathologic mediastinal lymph nodes or a lung tumor was required on the baseline computed tomography (CT) scan. Measurable disease according to the response evaluation criteria in solid tumors (RECIST) criteria was mandatory. Patients older than 64 years with poor prognostic factors [performance status more than 1 or lactate dehydrogenase (LDH) more than 2 times above the upper limit of normal] were excluded. Inclusion criteria were age between 18 and 75; performance status less than 3; adequate organ functions including hemoglobin

more than or equal to 6.0 mmol/liter, absolute neutrophil count (ANC) count less than or equal to 1,500/mm^3; platelet count more than or equal to 100,000/mm^3; bilirubin less than or equal to 40 mmol/L; international normalized ratio less of prothrombin time than 2 if not on antithrombotic treatment; and normal renal function. No other antineoplastic treatments for SCLC were allowed. Patients with a history of other malignant diseases except non-melanoma skin cancer and carcinoma in situ of the cervix were not eligible. Other exclusion criteria were pregnancy, lactation, active uncontrolled infection, or medical conditions unrelated to SCLC that—in the opinion of the treating physician—could expose the patient to unnecessary risks. Contraceptive measures were mandatory for fertile women. Written informed consent was required. The study protocol was approved by the regulatory authorities and ethical review boards. The study was conducted according to the declaration of Helsinki.

Patient Evaluation

At baseline, patients underwent the following evaluation: complete medical history including prior malignant diseases, physical examination, revision of the pathology report, weight, height, World Health Organization performance status, electrocardiography, chest radiograph, CT scan of the chest and upper abdomen (ultrasound study of the abdomen could substitute for abdominal CT scan), double-sided bone marrow aspiration with biopsy, bronchoscopy and/or mediastinoscopy, ^{51}Cr-ethylenediaminetetraacetic acid (EDTA) or creatinine clearance, complete blood count, biochemistry including LDH, alkaline phosphatase, aminotransaminases, bilirubin, prothrombin time, albumin, sodium, potassium, calcium, magnesium, creatinine, and dipstick urine analysis. Brain scans were not routinely performed.

Treatment

Treatment consisted of six cycles of topotecan 2.0 mg/m^2 on day 1 to 3 given intravenously (i.v.) over 30 minutes and cisplatin 50 mg/m^2 i.v. on day 3. Cycles were repeated every 3 weeks. Patients with progressive disease or no-change after three cycles went off study. Patients were hydrated with 1500 mL saline and 500 mL 10% mannitol over 2 hours and with 2000 mL saline over 4 hours before and after the administration of cisplatin, respectively. Antiemetics included a 5-HT$_3$ receptor antagonist, steroids, and metoclopramide or metopimazine according to standard procedures at the participating centers.

Dose modifications: Treatment on day 1 was withheld 1 week if ANC was less than 1,500/mm^3 or platelet count was less than 75,000/mm^3. If hematologic recovery was not reached after 1 week, patients went off study. Topotecan was reduced to 75% if one of the following events occurred: ANC nadir of 500/mm^3 or lower for more than 5 days; ANC nadir of 500/mm^3 or lower of any duration in combination with fever of more than 38.5°C or infection; platelet count nadir of 25,000/mm^3 or lower for more than 5 days. Patients went off study if renal clearance dropped below 40 mL/min or in the event of grade 3 or 4 oto- or neurotoxicity.

End Point Evaluation

The primary end points of the study were response rate and response duration. Response assessment was performed according to RECIST in solid tumors criteria. Confirmation of response was required minimum 4 weeks after the response was initially recorded. Response duration was defined as the time from the first day of treatment to documented progression or death due to SCLC in patients achieving a partial or complete response. Follow-up visits including medical history, physical examination, biochemistry, and chest radiograph were performed every third month. Secondary end points were toxicity, median and 2-year survival. Toxicity was graded according to National Cancer Institute Common Toxicity Criteria version 2.0. Survival was defined as the time from the first day of treatment to the date of death.

Statistics

Simons optimal two-stage design was used.[8] If the true response rate (complete and partial responses) was at least 70%, the regimen was to be regarded as active supporting further evaluation in phase III trials. No further development of the regimen was justified if the true response rate was less than 50%. A risk of 5% (α) of completing the study although the true response rate was lower than 50% was accepted. Furthermore, a probability of 20% (β) of rejecting the regimen even though the true response rate was at least 70% was allowed. Under these conditions, the trial should be stopped after the first stage if eight patients or less responded out the first 15 patients enrolled. The regimen was regarded as active and suitable for further clinical development, if 26 patients or more responded out of a total number of 43 patients enrolled. The method of Kaplan-Meier was used to estimate median response duration and overall survival. Patients who were lost for follow-up or died of causes other than progression were censored in the response duration analysis.

RESULTS

Patient Characteristics

From May 2001 to September 2003, 43 patients from six Danish centers were enrolled. Sixty-three percent of patients were male. Median age was 59 years. Seventy-nine percent of patients had performance status 0 or 1. All patients had elevated LDH, and in two thirds of the patients the LDH was more than twice the upper limit of normal (Table 1).

Compliance

A total of 219 cycles of chemotherapy was administered. Seventy-six percent and 83% of the planned doses of topotecan and cisplatin were delivered. All patients received at least one cycle of chemotherapy. Thirty-one patients completed all six cycles. Reasons for failure of completing the scheduled cycles were progressive disease ($n = 6$), toxicity ($n = 2$), both progressive disease and toxicity ($n = 1$), lack of clinical benefit due to mixed response ($n = 1$), fatal cardiopulmonal event ($n = 1$). One patient died after surgery for a non-malignant bowel obstruction.

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TABLE 1. Patient Characteristics

	No. Patients (*n*)	Percent of Patients (%)
Gender		
Male	27	62.8
Female	16	37.2
Performance status		
PS = 0	12	27.9
PS = 1	22	51.2
PS = 2	4	9.3
Unknown	5	11.3
LDH		
Normal	0	0
<2 × ULN	13	30.2
>2 × ULN	29	67.4
Unknown	1	2.3
Sodium		
Low	17	39.5
Normal	25	58.1
High	1	2.3
Median age (range)	59 (44–74)	

ULN, upper limit of normal.

Toxicity

Hematologic toxicity was frequent. Grade 3 and 4 anemia, neutrocytopenia and thrombocytopenia were recorded in 9.5%, 66.7%, and 21.4% of patients, respectively (Table 2). Six episodes of neutropenic fever were reported corresponding to a frequency of 2.7% of courses (6 of 219) or 14.0% of patients (6 of 43). No episodes of fatal sepsis occurred. A median of two blood transfusions were infused to a total of 24 patients. No patients required pooled platelets during the treatment. One patient went off study after two cycles due to hearing loss. Treatment was postponed in 7.3% of cycles because of toxicity. Dose reductions were necessary due to hematological and non-hematologic toxicity in 9.6% and 3.7% of cycles, respectively. Non-hematologic toxicity was mild and manageable (Table 3). Grade 3 and 4 toxicities were infrequent. The most frequent toxicity was nausea. The median decrease in GFR was 9.0 mL/min in 24 patients with both a pre- and posttreatment measurement of ^{51}Cr-EDTA acid-clearence available. Three patients had a Glomerular Filtration Rate below 50 mL/min posttreatment.

TABLE 3. Non-hematologic Toxicity

	Grade 1 + 2 (%[a])	Grade 3 + 4 (%[a])
Nausea/vomiting	66	5
Neurotoxicity	22	2
Ototoxicity	10	5
Allergy	2	2
Renal toxicity	24	0

[a] Percent per patient.

Six patients died while on treatment. Causes of death were obvious progressive disease in three cases. One patient with a central tumor died at home because of fatal hemoptysis. Platelet count was 61 the preceding day. The most likely cause of death was tumor invasion into pulmonary vessels. However, a causal relationship to therapy cannot be completely excluded. One patient with dyspnea and chest pain died 22 days after the first cycle of chemotherapy. The cause of death was probably pulmonary embolism based on a right bundle branch block on the electrocardiograph, elevated fibrin D-dimer and normal creatinine kinase and troponin T. One patient died 3 days after surgery for a bowel obstruction considered secondary to radiotherapy delivered 51 days before death. Immediately after the completion of the second cycles on day 4, radiotherapy (4 Gy in seven daily fractions) was delivered due to tumor involvement of the sacral nerve plexus. The patient developed irradiation induced colitis. The study treatment may have contributed to the severity of colitis and the fatal outcome due to the small time interval between chemo- and radiotherapy.

Efficacy

Based on intension-to-treat, the overall and complete response rates were 72.1% and 9.3%, respectively (Table 4). The median overall survival was 10.3 months (95% confidence interval, 8.6–12.0) (Figure 1). The 2-year survival rate was 8%. The median response duration was 7.0 months (95% confidence interval, 6.3–7.7). Twenty-three patients (53%) received second line therapy.

DISCUSSION

Ongoing DNA synthesis is a prerequisite for topoisomerase I induced cell death. Transient topoisomerase I induced

TABLE 2. Hematologic toxicity

Reference	Topotecan Dose (mg/m^2)	Cisplatin Dose (mg/m^2)	Grade 3/4 Anemia (%)	Grade 3/4 Thrombopenia (%)	Grade 3/4 Neutropenia (%)	Grade3/4 Leucopenia (%)
[a]Qouix et al.[18]	1.25 d 1–5	50 d 5	46.4	31.7	87.8	39.1
[b]Herzog et al.[11]	2.0 d 1–3	—	16	13	90	58
[a]Seifart et al.[17]	1.0 d 1–5	75 d 5	42.9	52.4		64.3
[a]Seifart et al.[17]	1.5 d 1–3	75 d 3	21.4	40.4		47.6
[a,c]Present study	2.0 d 1–3	50 d 3	9.5	21.4	66.7	

Hematologic toxicity per patient compared with other studies of topotecan followed by cisplatin or topotecan alone. All schedules were administered every 3 wk.
[a] chemo-naïve extensive disease SCLC.
[b] Recurrent ovarian cancer.
[c] No data available in one patient due to early death.

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TABLE 4. Response

	No. of Patients (*N*)	Percent of Patients (%)	95% CI
Complete response	4	9.3	0.6–18.0
Partial response	27	62.8	48.3–77.2
Overall response	31	72.1	58.7–85.5
No change	4	9.3	0.6–18.0
Progressive disease	1	2.3	0–6.8
Not evaluable	7	16.3	5.2–27.3
Total	43	100	—

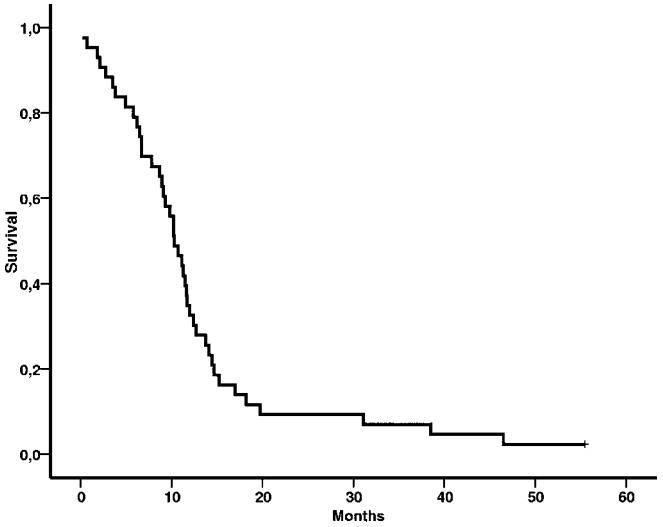

FIGURE 1. Overall survival. The median overall survival was 10.3 months (95% CI: 8.6–12.0).

DNA single strand breaks are converted into permanent and lethal DNA strand breaks when the DNA replication fork collides with a DNA single strand break.[9] These insights into the mechanism of action prompted clinical development of schedules with prolonged drug exposure including the now recommended 5-day schedule of topotecan. However, a 5-day schedule seems inconvenient and shorter schedules are warranted to reduce in-hospital stays for patients in the palliative setting. In ovarian cancer a 3-day monotherapy schedule has been developed using a dose of 2.0 mg/m^2 topotecan. Although no comparative trials have been performed, phase II data indicate that efficacy of the 3-day schedule is preserved compared with the conventionally used 5-day schedule.[10–12] Furthermore, the S phase specific topoisomerase II inhibitor, etoposide, seems active when given as part of a 3-day regimen. Thus, clinical data indicate that drug exposure can be reduced to less than 5 days with preservation of efficacy.

A decade ago it was established that the combination of a topoisomerase I inhibitor with a platinum results in a synergistic tumor cell kill in in vitro model systems.[4,13] Randomized trials have confirmed that the combination is very active and prolongs survival in cervical cancer[14] and extensive disease SCLC.[15] In an early phase I study, a 5-day topotecan schedule followed by cisplatin on day 1 was found safe and feasible.[16] However, the same group subsequently reported an unacceptable high rate of fatal sepsis.[5] Rowinsky et al. showed that hematologic toxicity is highly sequence dependent. In their phase I study, cisplatin was either given on day 1 or day 5 with topotecan given on day 1 through 5. The combination was far better tolerated when cisplatin was given after topotecan.[6] We later showed that the maximum-tolerated dose of topotecan with 50 mg/m^2 cisplatin on day 5 was equivalent to the recommended dose of topotecan as single agent i.e., 1.5 mg/m^2 topotecan.[7]

We now report a phase II study that integrate these two concepts, i.e., a shorter drug exposure and combination with cisplatin. A 3-day schedule was used with cisplatin on day 3. The regimen was feasible with 72% of all patients (31 of 43) completing all six cycles. Disease progression was the most frequent reason for interrupting treatment. The combination was safe. No episodes of fatal sepsis occurred. The frequency of grade 3 and 4 neutropenia (66.7%) compares favorable to 90% neutropenia and 58% leucocytopenia reported in recurrent ovarian cancer patients treated with 2.0 mg/m^2 topotecan in 3 days without cisplatin.[11] Presumably, the variation in myelosuppression reflects whether topotecan is given as first- or second-line treatment. Interestingly, thrombocytopenia was more frequent in our study (21.4%) and other studies[17,18] combining topotecan with cisplatin compared with second-line single-agent topotecan in the ovarian cancer population (13%).[11] The increased thrombocytopenia could be caused by a combined effect of cisplatin and topotecan. A German randomized phase II trial compared 3-day (1.0 mg/m^2 i.v.) with 5-day topotecan (1.5 mg/m^2 i.v.) followed by cisplatin (75 mg/m^2 i.v.) in chemo-naive SCLC patients with extensive disease.[17] Grade 3 and 4 thrombocytopenia and anemia in the 3-day arm of the German study were approximately double that seen in the present study (40.4% and 21.4% versus 21.4% and 9.5%) using a higher topotecan and lower cisplatin dose than in German study. Myelosuppression was reported as leukocyte and neutrofilocyte count in the two studies, respectively, which hampers a direct comparison. However, leucocytopenia of 47.6% in the German trial seems in the range of a neutropenia frequency of 66.7% reported in our study (Table 2). Again, the increased thrombocytopenia and anemia might be an effect of the higher dose of cisplatin used in the German trial. This hypothesis is in accordance with data showing that the degree of hematologic toxicity increases when topotecan and cisplatin are combined.[6] A response rate of 72% in the intension-to-treat population and a median survival of 10.3 months compares favorable to a response rate of 60% and median survival of 7.6 months in 3-day arm of the German study.[17] As the response rate reached in the present study was beyond the prespecified criteria, the combination seems suitable for further clinical development. Thus, the Danish Oncological Lung Cancer Group launched a nationwide phase III randomized trial that compares this regimen to a standard etoposide/platinum combination. A number of trials randomizing between a topo I and a topo II inhibitor in combination with a platinum have reached conflicting results. An impressive 3.4 months survival benefit favoring irinotecan/cisplatin compared with eto-

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poside/cisplatin in a preplanned interims analysis of 134 patients reported by the Japanese Cooperative Oncology Group (JCOG)[15] prompted North American investigators to initiate two confirmative trials. In a larger study with a slightly modified schedule, the encouraging Japanese results could not be confirmed.[19] The South West Oncology Group has completed a replicate trial that uses the exact same schedule as the JCOG trial and this trial has yet to be reported. In contrast, two European trials substituting cis- with carboplatin lend some support to the JCOG data. A slight but significant survival benefit of 1.3 months was found in the irinotecan arm of the Norwegian IRIS trial randomizing 210 patients with extensive disease.[20] A German phase II study randomizing 70 patients was extended to a phase III trial due to a significant increase in the median progression-free survival from 6 to 9 months in favor of the irinotecan/carboplatin arm.[21] In one of the largest randomized trials ever conducted in SCLC, oral topotecan in combination with cisplatin was non-inferior to intravenous etoposide/cisplatin with respect to survival.[22] The oral formulation of topotecan is claimed to be as efficacious as the intravenous formulation. However, comparisons of the two administration forms have only been done in the second line setting in two underpowered randomized studies.[23,24] Both the frequency of clinical benefit (35.9% versus 45.1%) and progression-free survival (11.9 versus 14.6 weeks) favored numerically the intravenous administration in the largest trial.[23] Thus, the role of first line intravenous topotecan in combination cisplatin remains to be determined. An ongoing Danish Oncological Lung Cancer Group trial aims to contribute to the resolvement of this question.

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