Epirubicin Weekly in Combination Chemotherapy with Cyclophosphamide and Vincristin in Untreated Small Cell Lung Cancer: A Phase II Trial

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Key Words

Small cell lung carcinoma

Epirubicin weekly with cyclophosphamide and vincristine

Summary

Thirty-three patients with untreated small cell lung carcinoma received 6 cycles epirubicin 30 mg/m² i.v. on days 1, 8, and 15, in combination with cyclophosphamide 1,000 mg/m² on day 1 and vincristine 2 mg i.v. on day 1 every 3 weeks. Thirty-one patients were evaluable concerning state of remission. Four out of 13 patients with limited disease had a complete, and 6 a partial remission, while 2 out of 18 patients with extensive disease had a complete and 8 a partial remission. The toxicity of this therapy regimen was very low. The results of this treatment did not differ significantly in comparison to the standardized treatment of small cell lung cancer, but it was easier to tolerate.

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Schlüsselwörter

Kleinzelliges Bronchialkarzinom

Epirubicin wöchentlich plus Cyclophosphamid und Vincristin

Zusammenfassung

33 Patienten mit unbehandeltem kleinzelligem Bronchialkarzinom erhielten 6 Zyklen Epirubicin 30 mg/m² i.v. an den Tagen 1, 8 und 15, kombiniert mit Cyclophosphamid 1000 mg/m² i.v. an Tag 1 und Vincristin 2 mg i.v. an Tag 1 in Abständen von 3 Wochen. 31 Patienten waren bezüglich des Remissionsstatus auswertbar. Von 13 Patienten des Stadiums «limited disease» erreichten 4 eine komplette Remission und 6 eine partielle Remission, während von 18 Patienten des Stadiums «extensive disease» 2 eine komplette Remission und 8 eine partielle Remission erzielten. Die Toxizität dieses Therapieverfahrens war sehr gering. Verglichen mit der Standardtherapie des kleinzelligen Bronchialkarzinoms unterschieden sich die Ergebnisse dieses Verfahrens nicht, die Verträglichkeit war jedoch besser.

Introduction

Today polychemotherapy is the treatment of first choice for most patients with small cell lung cancer (SCLC). Since the 1970s the most frequently used 3-drug regimen adriamycin (A), cyclophosphamide (C) and vincristin (O) achieved response rates of 60–90% and a median survival of about 13–15 months in limited disease (LD) and 9–11 months in extensive disease (ED) [2]. Alternating treatment using 5 or more agents seems to be more effective but toxic reactions are of a higher degree as well. Since there were no more remarkable improvements of therapeutical outcome for patients with SCLC, the development of a protocol that produces fewer toxic side effects but maintains previously achieved results has been attempted [4].

Epirubicin, the 4'-epi derivative of adriamycin, suggested the same effectiveness with less toxicity compared to adriamycin [3]. Using a weekly low-dose regimen of adriamycin seemed to be similarly effective but less toxic than the drug given every 3 weeks [5]. In the present phase II trial we investigated a regimen with epirubicin (E) given weekly in combination with cyclophosphamide (C) and vincristin (O) applied during a 3-week interval.

Patients and Methods

Thirty-three untreated patients with histologically confirmed SCLC, measurable disease.

Karnofsky performance status (KPS) of > 60 and an adequate bone marrow function entered the trial between

December 1986 and September 1987. Treatment consisted of 6 cycles E 30 mg/m² i.v. days 1, 8 and 15, C 1,000 mg/m² i.v. day 1, and O 2 mg i.v. day 1 administered in 3-week intervals. If there was not at least a partial remission (PR) after 2 cycles, therapy was changed to ifosfamide and etoposide. Drug application was delayed 1 week if the white blood cell count (WBC) was < 4.0/nl or platelet count was < 100/nl at day 21. Drug dosage was reduced if a patient remained leuko- or thrombopenic after treatment delay. Radiotherapy consisted of 46 Gy chest irradiation after 6 cycles in LD and 30 Gy prophylactic cranial irradiation (PCI) for patients who achieved complete remission (CR). Tumor response and toxicity were assessed using standard criteria for CR, PR, no change (NC), progressive disease (PD), and World Health Organisation (WHO) toxicity criteria according to grade 0–4.

Results

One patient died 3 days after the start of therapy due to the disease. Another refused further chemotherapy after the first cycle. Of the 31 eligible patients (28 male, 3 female) 13 had LD and 18 ED. The median age was 59 years (range 40–73 years). All patients were ambulatory and had KPS 80–100. From 2 to 7 cycles of ECO were administered depending on therapy response. Responders received a 360–615 mg/m² cumulative dose of E. In the LD group, 4 of the 13 evaluable patients achieved CR and an additional 6 patients PR (CR and PR 77%). In 2 cases NC and in 1 case PD were observed in this group. In 10 out of 18 ED cases (56%) we noticed a good response (2 × CR, 8 × PR). There were 7 patients with NC and 1 with PD in the ED group. Two male patients with LD who

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Table 1. Toxicity data (WHO) of 31 patients with SCLC treated by ECO weekly

WHO grade

0 12 3 4

Hematological

WBC

5

6

8

11

Platelets

31

-

-

-
Hemoglobin
15
13
3
-
Alopecia
-
2
5
24
Nausea/vomiting
7
20
2
2
Paresthesia
27
3
2
-
Infections
27
1
2
1
Fever
27
2
1
1
Stomatitis
30
-
1
-
Hematuria
30
-
1
-
Deterioration of

consciousness

28

3

-

-

Table 2. Polychemotherapy in SCLC. Comparison of our own results (ECO weekly) with data from the literature

Study	ECO weekly [1]	STD-ECO [2]	ACO alternating [2]	9 Agents
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received 6 cycles ECO, chest irradiation and PCI are alive 31 and 32 months after the start of therapy without evidence of disease. All other patients have relapsed and died in the meantime. Patients with LD had a median survival of 15 months, a median progression-free survival of 8 months, and 23 % of this group survived 2 years and more. In the ED group median survival was 10 months with a median progression-free survival of 4 months, and a 2-year survival of 11%. The toxicity of the regimen was mild. Neither treatment-related fatalities nor any life-threatening complications were noticed. For all side effects observed see table 1. We did not see any cases of cardiotoxicity, cutaneous lesions, diarrhea or constipation due to the treatment.

Discussion

The median survival and response rate of the patients treated with the ECO weekly regimen for both groups LD and ED

seem to be similar to those of today's standard therapies. Drings et al. treated 51 patients with 6 cycles ECO, E = 70 mg/ m² every 3 weeks (STD-ECO) [1]. In a large German multi-center trial Havemann et al. randomized 302 eligible patients into a standard treatment arm with 8 cycles ACO and an alternating chemotherapy arm with 9 different agents during 8 cycles. Table 2 compares the results of our study, of the STD-ECO study and both the ACO and the alternating therapy arm of the multicenter trial. The side effects of the investigated regimen seemed to be less severe than those of the compared therapy forms. During the multicenter trial 1.7% of the patients in the ACO arm and 5.3% in the alternating therapy arm died in relation to the treatment. Life-threatening complications were observed in 1.3% of patients under ACO, in 2% under STD-ECO and in 4% after the alternating therapy. No such complications were seen in the ECO weekly study. Hematological toxicity was severe, with 18% and 25% WHO grade 4 leukocytopenia in the ACO and the alternating arm respectively. Only in 1 patient (3.2%) was WHO grade 4 leukocytopenia seen after ECO weekly application. From 4 to 7% of the patients in the STD-ECO, the ACO and the alternating therapy study suffered from severe cardiotoxicity due to the treatment. We conclude that the ECO weekly regimen is an effective form of treatment in SCLC with fewer toxic reactions than today's standard regimens. To confirm these results further studies are required.

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