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Short communication

Phase II study of high-dose aclarubicin in previously treated patients with small-cell lung cancer

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Aclarubicin is one of the antitumor anthracyclines (aclacinomycin A) isolated from *Streptomyces galilaeus* by Oki et al. in 1975 [9]. Preclinical evaluation of aclarubicin has revealed several important differences in the drug's properties relative to the classic anthracyclines doxorubicin and daunorubicin. Cellular uptake of aclarubicin occurs more rapidly [11], and in contrast to the classic anthracyclines, aclarubicin does not stimulate topoisomerase II-mediated DNA breaks [6]. Furthermore, only limited, if any cross-resistance with aclarubicin has been demonstrated in the two well-defined doxorubicin-resistant phenotypes, P-gp MDR (P-glycoprotein multidrug-resistant) and at-MDR (altered topoisomerase MDR) cells [4, 5]. Aclarubicin given on a single-bolus schedule has not shown clinically relevant activity against solid tumors [1, 2, 7]. In contrast, the drug has demonstrated activity against leukemia. However, these trials have involved the administration of aclarubicin on prolonged schedules over 3–5 consecutive days and at higher cumulative doses [3, 8, 10, 12]. The present report describes a phase II trial of high-dose aclarubicin given on a 3-day treatment schedule to previously treated patients with small-cell lung cancer.

Patients and methods

Included were patients with small-cell lung cancer who fulfilled the following entry criteria: (a) a histologically confirmed diagnosis, (b) relapse or progression of disease after first-line chemotherapy, (c) the presence of at least one evaluable lesion, (d) a WHO performance status of ≤ 2 [13], (e) a WBC of $\geq 3 \times 10^9/l$ and a platelet count of $\geq 100 \times 10^9/l$, (f) verbal informed consent, and (g) no history of cardiac disease or signs of congestive heart disease.

Aclarubicin, kindly supplied by Lundbeck (Copenhagen, Denmark), was dissolved in 200 ml isotonic saline and given as an i. v. infusion over 1 h daily for 3 days. The initial dose in the first four patients was 80 mg/m^2. Due to severe myelotoxicity, the dose was subsequently reduced to 70 mg/m^2 (ten patients). Toxicity was assessed by blood counts at least twice a week, and treatment was repeated when the WBC was $\geq 3 \times 10^9/l$ and the platelet count was $\geq 100 \times 10^9/l$. Dose modifications were based on the duration of leuko-/thrombocytopenia; if leuko-/thrombocytopenia persisted for >7 or >14 days, the dose was reduced to 50 or 35 mg/m^2, respectively.

Results

A total of 14 patients were entered in the study. The limited disease:extensive disease (LD:ED) ratio and the ratio of men to women were 1:1 and 10:4, respectively. The median age of our subjects was 55 years (range, 42–66 years). All patients had previously been treated with a combination of drugs, including alkylating agents and epipodophyllotoxins; eight subjects had additionally received doxorubicin. The median number of drugs previously given to each patient was 7 (range, 3–10), and 6 individuals had received ≥ 9 different agents prior to the present study. Eight patients showed progression of residual tumors and six were in first relapse. The median interval between prior chemotherapy and aclarubicin treatment was 3 months (range, 0–10 months). The median number of aclarubicin courses completed was 2 (range, 1–5), and the median total cumulative aclarubicin dose was 360 mg/m^2 (range, 210–810 mg/m^2), with four patients receiving >600 mg/m^2.

One partial response lasting 11 weeks was observed in a patient previously treated with doxorubicin. This subject completed three cycles of 70 mg/m^2 aclarubicin (cumulative dose, 630 mg/m^2); after the last course, the patient developed permanent ECG changes with inverted T-waves and the aclarubicin treatment was stopped. Four individuals exhibited stable disease; therapy was discontinued due to nausea in two of these subjects after the first and the second course, respectively. In the other two cases, treatment was discontinued after cumulative doses of 810 and 690 mg/m^2, respectively, had been received. Two patients with liver metastases died of hemorrhagic diathesis associated with leuko- and thrombocytopenia at 10 and

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Table 1. Numbers of patients with small-cell lung cancer who developed aclarubicin-induced toxicity after the first treatment course[a]

Toxic effect	WHO grade				
	0	1	2	3	4
Leukopenia	0	1	2	2	9
Thrombocytopenia	0	0	0	1	13
Hemorrhage	1	2	6	4	1
Fever	1	2	7	3	–
Mucositis	5	5	1	–	–

[a] $n = 14$ patients

12 days after the first course, respectively. Seven subjects developed progressive disease. Myelosuppression, especially thrombocytopenia, was severe in all patients (Table 1).

Discussion

In a recent phase III trial, aclarubicin was found to be superior to daunorubicin in previously untreated patients with acute myeloid leukemia [3]. Preclinical data show that aclarubicin is active against small-cell lung-cancer (SCLC) cell lines that are inherently resistant to classic anthracyclines [4]. Clinically, a lack of cross-resistance to aclarubicin has been suggested in patients with acute myeloid leukemia; a complete remission rate of 18% was achieved using aclarubicin at a dose of 80 mg/m^2 for 3 days in a phase II trial in patients with daunorubicin-refractory acute myeloid leukemia [10].

We chose a similar high-dose schedule for the present study, as two reports on acute myeloid leukemia have demonstrated that cumulative doses of >300 mg/m^2 are required to obtain remissions [8, 12]. As shown in Table 1, this treatment was very myelotoxic. Of 12 evaluable patients, 1 achieved a partial remission. As the 95% confidence intervals were 0.2%–38%, antitumor activity for high-dose aclarubicin cannot be completely excluded; however because the regimen was extraordinarily toxic and only one partial response of short duration was obtained, the investigation was closed. Our rationale for using high-dose treatment was based on previous results obtained in patients with acute myelocytic leukemia. In agreement with these findings, the patient who achieved a partial remission had been given a high cumulative dose of aclarubicin (630 mg/m^2) in three cycles without dose reductions. In comparison, the median cumulative dose received by the other subjects was 360 mg/m^2 (180 mg/m^2 per cycle). In this context, it is noteworthy that Kramer et al. [7] and Abeloff et al. [2] gave 100 mg/m^2 per cycle to 14 and 25 evaluable patients with SCLC, respectively. The latter group reported severe hematological toxicity in 44% of the subjects. Moreover, no remissions were obtained in these 39 patients with SCLC. Considering these findings together with the present results, aclarubicin has shown no evidence of activity when given at doses producing acceptable toxicity to previously treated patients with SCLC.

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