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Epirubicin in Previously Untreated Patients with Small Cell Lung Cancer: A Phase II Study by the EORTC Lung Cancer Cooperative Group

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Epirubicin 110 mg/m² was administered intravenously every 3 weeks to 41 elderly and/or unfit, previously untreated patients with small cell lung cancer (SCLC). There were three complete responses, 16 partial responses and 14 treatment failures, with a response rate of 57% in 33 evaluable patients. The main toxicity was haematological, characterised by leukopenia and, less frequently, thrombocytopenia and anaemia. There were three toxic deaths due to infection occurring during leukopenia. Non-haematological side effects were alopecia, nausea, stomatitis and diarrhoea. WHO grade 2 cardiac toxicity was seen in 3 patients after a cumulative dose of more than 740 mg/m². In conclusion epirubicin is an active agent in untreated SCLC.
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INTRODUCTION

CHEMOTHERAPY achieves high response rates in small cell lung cancer (SCLC) leading to prolonged survival. However, less than 10% of patients can actually be cured with current combination chemotherapy and no substantial improvement has been obtained over the past decade. Therefore, there is an urgent need for new active drugs in this disease.

Testing new drugs in previously heavily treated patients may be misleading as potentially active drugs may be missed due to a development of broad drug resistance [1].

Elderly patients are rarely included in clinical trials [2] although they represent a large proportion of the population of patients with SCLC. It seems reasonable to treat these patients with "less toxic" chemotherapy, for example with a single agent [3]. In addition, the poor long-term results of treatment achieved in extensive SCLC with virtually no chance of cure, allow the inclusion of this category of patients without prior treatment in trials of investigational agents [4].

Epirubicin is a synthetic analogue of doxorubicin produced by structural modification of a aminosugar moiety of doxorubicin [5]. In experimental systems, epirubicin is less cardiotoxic than doxorubicin [6], and this has partially been confirmed in a prospectively randomised study of epirubicin vs. doxorubicin in anthracycline-naïve patients with advanced breast cancer [7].

Phase I trials of epirubicin recommended a dose of 70 mg/m² every 3 weeks. However it has been demonstrated that much higher doses can be given in good-risk patients [8]. We investigated the efficacy and toxicity of epirubicin in untreated SCLC patients at a dose of 110 mg/m².

MATERIALS AND METHODS

All patients were required to have histologically and/or cytologically confirmed SCLC, not to be candidate for curative surgery or radiation therapy, to have measurable or evaluable lesions, or performance status according to the WHO scale <4, an age >70 or younger if considered unfit for conventional combination chemotherapy. Staging include thorax chest X-ray, blood cell count and chemistry in all patients and non-invasive staging procedures were required in order to properly stage the disease. Complete blood cell counts were repeated weekly during the first two cycles and chest X-ray and chemistry every 3 weeks. At the start of treatment, patients were required to have a white blood cell (WBC) count over 4×10^9/l, platelets over 100×10^9/l, bilirubin less than 25.6μmol/l, creatinine less than 132μmol/l. Patients with prior chemotherapy or prior radiation therapy including all areas of measurable or evaluable disease, with brain or leptomeningeal involvement, with previous or concurrent other malignancy were ineligible. Patients who were at poor medical risk related to active cardiac disease were also ineligible.

Epirubicin was administered at a dose of 100 mg/m² every 3 weeks by rapid intravenous injection through the tubing of a freely running saline infusion. Dosage adjustments were made according to haematological tolerance (Table 1). Drug administration was postponed by one week if WBC were less than 4×10^9/l and/or platelets were under 100×10^9/l. The dose of epirubicin was reduced to 50 mg/m² if bilirubin increased to >2 mg/dl and stopped if it reached levels of >4 mg/dl.

Response and toxicity were evaluated according to the WHO criteria [9]. Response was assessed after two cycles of epirubicin unless obvious progressive disease occurred at an earlier stage.

Duration of response and survival from therapy commencement were calculated according to the Kaplan–Meier method [10].

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Table 1. Dosage adjustments according to the nadir of WBC and/or platelets between each course

WBC $\times 10^9$/l	Platelets $\times 10^9$/l	Dose (mg/m^2)
> 2.5	> 100	130
2.0 – 2.499	75.0–99.999	115
1.0 – 1.999	50.0–74.0	80
< 1.0	< 50.0	50

RESULTS

41 patients entered the study between July 1985 and April 1989 from 12 institutions. Of these 41 patients, 35 were more than 70 years old, 2 were less than 70 years old but unfit (i.e. with a performance status of 3 on the WHO scale), 4 were less than 70 years old and suitable for conventional combination chemotherapy and were included based on local institutional policy.

All patients were eligible. The characteristics of the 41 patients are summarised on Table 2. There were 3 patients totally inevaluable due to one refusal after one course with no toxicity data, two major violations of protocol (1 patient received conventional combination chemotherapy instead of epirubicin, 1 patient received 59% of the dose of epirubicin). 5 more patients are excluded from analysis of activity, because of lack of measurement or evaluation in one, early toxic deaths due to infection in 2, early deaths apparently unrelated to the malignant disease in 2 patients. 1 patient is excluded from analysis of toxicity (early death with no toxicity data), 5 are excluded from analysis of haematological toxicity (no nadirs).

Among the 33 patients evaluable for response there were 3 complete responders (2 with limited disease, 1 with extensive disease), 16 partial responders (7 with limited disease, 9 with extensive disease). There were 14 non-responders (5 with limited disease, 9 with extensive disease). Among these 14 non-responders, there were 4 early deaths due to disease progression. The overall response rate was 57% (C.I.: 39.2–74.5%). It was 46% if all eligible patients are considered.

Table 2. Characteristics of the 41 patients

Age	Median range	74 53–84
Sex	M/F	36/5
ECOG PS*	0	5
	1	12
	2	16
	3	7
Weight loss	< 1 %	16
	1–5 %	7
	6–10 %	11
	unknown	7
Extent of disease*	limited	18
	extensive	22
Metastatic sites	Bone	9
	Liver	10
	Pleura	6
	Other	7

* 1 patient not evaluable because of major violation of protocol had unknown PS and extent of disease.

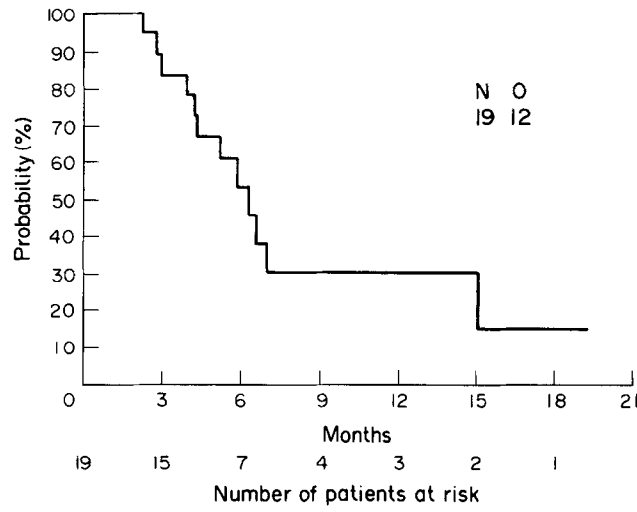

Fig. 1. Duration of response

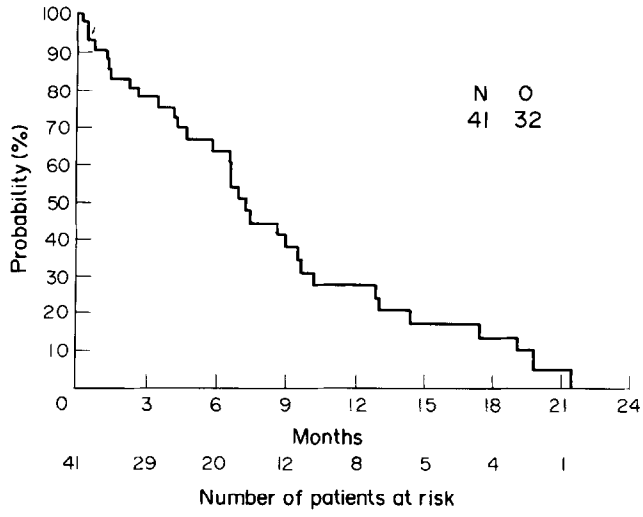

Fig. 2. Duration of survival

Median duration of response was 6.05 months (range 2.2—–19.25) (Fig. 1). Median survival time of the whole group was 6.61 months (Fig. 2)

A total of 172 courses were administered (median: 4, range 1–9). The median total dose of epirubicin was 436 mg/m^2 (range 110–998). The median interval between courses was 24 days (range 20–49). The doses were reduced in 34 cycles. Delays and dosage reductions were all due to haematological toxicity. Dose could be increased to 130 mg/m^2 only in 5 patients (and 17 cycles).

The main toxicity was haematological, characterised by leukopenia and less frequently thrombopenia and anaemia (Table 3).

Table 3. Haematological toxicity (32 evaluable patients)

WHO grade*	0	1	2	3	4
Leukopenia	2*	4	10	12	4
Thrombocytopenia	25	3	2	2	—
Anaemia	13	13	5	—	1

*Number of patients affected.

The median nadir of WBC was 1.9×10^9/l (range 0.3–5.5), it was 152×10^9/l (range 25–555) for the platelets. There were 3 toxic deaths due to infection occurring during leukopenia.

Non-haematological toxicity was mainly alopecia (38% grade 3), emesis (11% grade 3) and mild stomatitis (22%) and diarrhoea (24%). Cardiac toxicity grade 2 was observed in 3 patients with a cumulative dose of epirubicin > 740 mg/m^2. 1 patient, aged 74 died of cardiac failure 4 months after having received a total dose of 880 mg/m^2 (9 courses). The treatment was stopped due to the development of an atrial flutter and a mediastinal radiotherapy was then conducted.

DISCUSSION

Our study confirms epirubicin to be an active agent in untreated SCLC. Previously reported studies with similar schedules showed response rates from 33 to 57% with epirubicin in previously untreated patients with extensive SCLC [11–14]. The response rate may be slightly overestimated in our study due to the number of inevaluable patients. The somewhat high inevaluability rate in this study is likely to be due to the inclusion of elderly and unfit patients who are more exposed to die early and refusal of therapy and/or necessary investigations in order to assess response.

With lower doses of epirubicin, responses were fewer [15, 16], and responses in previously-treated patients has been low [17].

Anthracyclines and their analogues exhibit a steep dose–response curve in animal tumour, *in vitro* systems and in human neoplasms as well [18, 19],but its clinical use is limited by the resulting cumulative dose-limiting cardiotoxicity. In none of the studies using high doses epirubicin cardiotoxicity has been the dose-limiting side-effect although Giaccone *et al.* [17] reported substantial cardiac toxicity (partly related to prior treatment with anthracyclins). The cumulative dose which is thought to be the limit for cardiac toxicity is 900–1000 mg/m^2 [7]. In our study, although most of the patients were at poor medical risk due to their age, cardiac toxicity has been manageable occurring in 3 patients at a cumulative dose >740 mg/m^2. The death of 1 of the 3 patients is probably related to cardiotoxicity of epirubicin enhanced by subsequent radiotherapy. The cardiotoxicity observed with epirubicin given as a monotherapy at high dose to elderly or unfit patients with SCLC certainly do not reflect what would be observed with epirubicin part of a standard combination and given at the same dose as its parent compound.

The maximum tolerated dose in untreated patients is now thought to be 150–165 mg/m^2, neutropenia and stomatitis being the dose limiting toxicities [8].

Median survival time of 6.6 months in our study is shorter than other published series [20] of extensive stage small cell lung cancer, although Banham *et al.* [12] reported very similar survival of his series of patients treated with 120 mg/m^2 and whose criteria of eligibility were somewhat similar to ours. This poor survival may be related to the high age of most of the patients. Elderly patients with small cell lung cancer have been reported to have a poor survival [21], but very little is known about the reasons for this poor survival. Under treatment of the elderly due to the widespread conception of poor tolerance to chemotherapy or radiotherapy [2] results in the fact that it is not certain that high age is an adverse prognostic factor *per se* [22].

Even if high age of our group of patients may explain the poor survival, one cannot be sure that using standard combination therapy would not have resulted in a better survival. In a recent paper dealing with ethical dilemmas encountered when evaluating new drugs in patients with small cell lung cancer [23], McCullen recommended safeguards for phase II studies in previously untreated patients with small cell lung cancer in order to avoid that the patients who fail to respond to the new treatment suffer from having received it. A new agent which does not give a response after one course in small cell lung cancer is not likely to be active with a second course and patients who fail to respond after a single course should be switched to a standard combination. Of the four comparable phase II studies of epirubicin in SCLC [11–14], only one [11], was designed to switch patients who failed to respond after 1 cycle or who failed to achieve complete response after 4 cycles to a combination chemotherapy (cisplatin plus etoposide). Median survival time in this study including patients with extensive stage disease was 8.3 months. Anyway in the type of population which was included in our study, such a switch to an aggressive combination was impossible.

In conclusion, epirubicin is an active agent in SCLC. Its use in combination with other agents as first-line therapy is possible, provided that any advantage over its parent compound, doxorubicin, remains to be proven at the schedule and doses usually applied in SCLC. Despite the good response rate, the poor overall survival suggests the need to develop strategies for elderly and/or unfit patients with SCLC.

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Early Assessment of a New Anticancer Drug Analogue — are the Historical Comparisons Obsolete? The French Experience with Pirarubicin

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Data of all phase II studies of pirarubicin (THP-doxorubicin) have been analysed for toxicity or activity in breast cancer and compared with published reports on doxorubicin, epirubicin or mitoxantrone used as single drugs. A graph of the 95% confidence intervals for each event was used. The results suggest that pirarubicin is as effective as other intercalating drugs in breast cancer and grossly better tolerated than doxorubicin, especially alopecia and cumulative cardiotoxicity. The equimyelotoxic doses of each drug were also estimated. The methodology and the validity of such historical comparisons is discussed: they cannot replace prospective randomised phase III studies, and do not allow definitive conclusions. However, most comparative trials of anticancer drug analogues cannot answer the right questions because their objectives are not adequate (especially for equiefficacy). But early evaluation by historical comparisons can help the conception of phase III studies.
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INTRODUCTION

AFTER THE phase II trials have shown efficacy and described main toxicities, the development of a new anticancer drug reaches a pivotal point. It is necesary to compare it with the standard drugs, when they exist or to no specific treatment when such drugs do not yet exist. This comparison has to be done by mean of comparative, randomised phase III trials.

Such trials are time-consuming, costly and need a heavy organisation for collecting and treating data by the sponsor. That is the reason why, before starting the phase III trials, a thorough examination of the data available from the phase II studies should be recommended, to target the most adequate population of patients and to give the optimal dose of the drug, in order to ask the right questions and to give oneself the means to answer them, with the ethically acceptable price for the patients.

Historical comparisons, despite all statistical objections, are the only manner to place early the new drug. They cannot, obviously either substitute themselves to the phase III studies, or give definitive conclusions, but, on the other hand, they can valuably help their conception.

Pirarubicin (tetrahydropyranyl [THP] doxorubicin) is an anthracycline, selected on preclinical data which had shown an efficacy superior or equal to the mother compound doxorubicin with less toxicity [1]. We report here the methodology and the results of the early evaluation of THP, using phase II data of the drug, compared with historical data concerning DOX and other intercalating drugs effective in breast cancer (i.e. epirubicin and mitoxantrone).

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