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Combined treatment in advanced stages (IIIb-IV) of non-small cell lung cancer

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Abstract. – **Chemotherapy regimens based on platinum represent the reference standards in Non-Small Cell Lung Cancer (NSCLC) and when it is associated with radiotherapy and/or surgery (combined treatment) it improves survival of patients. Aim of this study was to estimate the efficacy of chemotherapy, based on high-dose epirubicin plus cisplatin, associated with surgery and/or radiotherapy. Twenty-four inoperable NSCLC patients (15 pts in stage IIIb and 9 in stage IV) were treated with epirubicin (120 mg/m²) plus cisplatin (60 mg/m²), every three weeks for at least 3 cycles up to a maximum of 6. A total of 109 treatment cycles (epirubicin plus cisplatin) were administered and two of 24 patients achieved full response (CR), 9 showed partial response (PR), for an overall response rate of 45.8%, 8 patients (33.4%) achieved stable disease (SD) and 5 (20.8%) progressive disease (PD). Leukopenia aroses in 81.9% of the cycles, anaemia in 36.6% and thrombocytopenia in 14%. After chemotherapy, nausea/vomiting was present in 33.3% of patients, while in a small number of cases there were also mucositis, diarrhea, fever, phlebitis, transaminase increase and electrocardiographic anomalies. Upon entry, at the end of therapy patients underwent restaging (CT, bronchoscopy, bone scintiscan) to evaluate the possibility of surgical resection; 15 out of 24 patients completed treatment with radiotherapy (40-60 Gy) and then were re-evaluated for surgery. Five patients underwent complete surgical resection of the neoplasia (4 after chemotherapy and one after radiotherapy). After 1 year survival was 66.6% for all patients. Combined treatment in advanced NSCLC showed a good response and survival after 1 year.**

Key Words:

Non-small cell lung cancer, Epirubicin, Cisplatin, Radiotherapy, Surgery, Combined therapy.

Introduction

Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer death. More than 70% of cases are in advanced and inoperable stage at diagnosis[1]. Chemotherapy in locally advanced or metastatic NSCLC has shown to bring mild benefit on survival compared to supportive therapy only[2]. The therapeutic regimens based on platinum represent the reference standards and this drug has been administered in association with other products (etoposide, gemcitabine, vindesine, mytomicyn, epirubicin, taxanes etc.) in an attempt to control the disease[3,4]. In the last few years, chemotherapy has also had a role as preoperative treatment (neoadjuvant therapy) to reduce the tumor mass and the local-regional metastasis (lymph nodes), improving resectability. This schedula is completed by post-operative treatment (adjuvant chemotherapy)[5]. In advanced stages (IIIb and IV) usually chemotherapy alone gives poor results. In these cases, concomitant or sequential radiotherapy could improve survival[6-9].

Epirubicin (EPI) is one of the drugs studied during the last few years in combination with cisplatin (CP) in NSCLC treatment. EPI is an antibiotic that belongs to the group of anthracyclines and it is a doxorubicin epimer; it mimics a DNA intercalant agent as does doxorubicin, but epirubicin, at the same doses as doxorubicin, is less myelotoxic and has lower cardiotoxic effect than doxorubicin[10]. This has allowed to use this drug in NSCLC treatment at higher dosages than doxorubicin, revealing an antitumoural activity also in monotherapy[11-14]. EPI was also evaluated at high doses combined with cisplatin and

other chemotherapic agents showing a mild to moderate therapeutic effect on survival[15-17].

The aim of the present study was to evaluate the efficacy of CP plus EPI in the treatment of advanced NSCLC (stages IIIb and IV) combined with surgery and/or radiotherapy.

Materials and Methods

Twenty-four consecutive patients with histologically proven NSCLC at stage IIIb or IV were enrolled. Eligibility criteria for the inclusion in the study were: patients aged less than 70 years, life expectancy more than 3 months, performance status of 0 to 2 on the Eastern Cooperative Oncology Group (ECOG), a weight loss not exceeding 5% during the previous 3 months and the presence of at least one lesion measurable or assessable by CT. Patients had normal haematological parameters (WBC > 4000/mm^3, neutrophil cells > 2000/mm^3, haemoglobin level > 11gr/dl, platelets > 100.000/mm^3) with adequate renal (creatinine < 1,25 × N, BUN < 1,25 × N) and hepatic function (bilirubin < 1,25 × N, transaminase < 1,25 × N), and no evidence of cardiac diseases on ECG. A history of congestive heart failure, uncontrolled hypertension, arrhythmias and myocardial infarction were considered exclusion criteria. Patients who had received previous surgical, radiation or other chemotherapic treatment were excluded from the study.

The treatment scheme consisted of intravenous administration of epirubicin at the dose of 120 mg/m^2 plus cisplatin at the dose of 60 mg/m^2 on the same day, every 3 weeks for at least 3 cycles up to a maximum of 6 cycles. Antiemetic drugs were administered to all patients. Patients were assessed for haematological toxicity on day 14 of each cycle. Treatment with granulocyte colony stimulating factor (G-CSF) was administered (filgrastim 5 mg/kg/die by subcutaneous injection for three days) if at nadir patients had WBC < 2000/mm^3; epoetin α was administered by a subcutaneous dose of 10.000 UI on alternate days if haemoglobin was less than 10 gr/dl until normal values were restored. The planned dosage of two antiblastic drugs was reduced to 75% of the established dose in the presence of persistent haematological toxicity (grade 3 or 4), appearance of febrile neutropenia or other non-haematological toxicity (grade 3 or 4): the median dose reduction was 13,2%. For the same reasons the administration of some cycles could be delayed for a few days and the mean interval between two cycles was 25 days. Cardiac activity was studied by ECG and by echocardiography if necessary.

All patients were evaluated by computerized tomography (CT), bone scintiscan, fiberoptic broncoscopy at entry and at the end of chemotherapy. All adverse events reported by patients or detected by clinical exams were recorded and classified under the WHO scoring system[1]). At the end of chemotherapy the possibility of surgical resection was evaluated again; otherwise, inoperable patients who had a partial response or stable disease with a good performance status (0-2 ECOG) underwent radiotherapy (RT) on tumor or mediastinum at an interval of 4 weeks between chemotherapy and radiotherapy. The radiotherapy dose administered was 40-60 Gy according to a fractionated schedule. After 30 days, CT, bone scintiscan and fiberoptic bronchoscopy were repeated and patients re-evaluated. After one year from diagnosis survival for all patients was established.

Results

Twenty-four patients entered this study (20 males and 4 females), median age 64.9 years (from 55 to 70) and a median performance status according to the ECOG scale of 1 (range 0 to 2). Disease stage was IIIb in 15 cases and IV in 9 cases. The histological diagnosis was squamous cell carcinoma in 9 patients, adenocarcinoma in 15 patients.

Overall, 109 cycles of chemotherapy were administered with a mean of 4.5 cycles for each patient (range from 3 to 6). Two of 24 patients (8.3%) achieved complete response (CR) and 9 (37.5%) partial response (PR), which accounted for an overall response rate of 45.8%. Stable disease (SD) occurred in 8 patients (33.4%) and 5 of 24 patients (20.8%) had progressive disease (PD) /(Table I).

Subdividing patients according to the stage of disease, we observed in stage IIIb (15 pts) 1 complete response (CR) and 5 partial re-

Table I. Overall response rate after chemotherapy (epirubicin + cisplatinum) in 24 NSCLC pts .

	Pts n°	CR+PR (%)	SD (%)	PD (%)
Overall	24	2+9 (45.8%)	8 (33.4%)	5 (20.8%)
Staging				
stage IIIB	15	1+5 (40%)	5 (33.3%)	4 (26,7%)
stage IV	9	1+4 (55.6%)	3 (33.3%)	1 (11.1%)
Histology				
Epidermoid	9	1+3 (44.5%)	3 (33.3%)	2 (22.2%)
Adenocarcinoma	15	1+6 (46.7%)	5 (33.3%)	3 (20%)

Complete Response (CR); Partial Response (PR); Stable Disease (SD); Progressive Disease (PD).

sponses (PR), for an overall rate of 40%; 5 pts (33.3%) revealed stable disease (SD) and 4 pts (26.7%) showed a progression of the disease (PD).

In the 9 patients at IV stage, there was an objective response in 5 cases (55.6%) (1 complete response and 4 partial); stable disease (SD) occurred in 3 patients (33.3%) and only 1 patient (11.1%) showed a progression of disease (PD) (Table I).

In regard to histological type, we found that 1 pt, out of 9 patients with squamous cell carcinoma, achieved complete response and 3 patients partial response with an overall remission rate of 44.5%, in 3 out of 9 patients (33.3%) was evidenced stable disease and in 2/9 (22.2%) a progression of disease. In 7 patients, out of 15 with adenocarcinoma, it was observed 1 CR e 6 PR, with a rate of 46.7%; 5 patients were with stable disease (33.3%) and 3 patients with a progression of disease (20%).

At the end of chemotherapy, 4 patients were considered eligible for surgery and they underwent complete surgical resection (1 pts at stage IV, 3 pts at stage IIIb).

After chemotherapy, the main toxicity noticed was haematological (Table II). The incidence of side effects per cycles administered was leukopenia 81.9% (WHO grade 3 or 4: 21.3%), anaemia 36.6% (in none WHO grade 3 or 4), whereas thrombocytopenia occurred in 14% of cycles (WHO grade 3 or 4: 1.1%) (Table II).The main non-haematological toxicity was represented by nausea/vomiting, which occurred in 8 patients (33.3%), with a WHO grade 3 only in two cases (8.3%). In 3 patients ECG revealed tachycardia > 115/min and in 2 it revealed atrial tachyarrthmia but these disorders were transient. Febrile neutropenia was observed in 3 cases. Other side effects were mucositis (3 pts), phlebitis (2 pts) and diarrhoea (2 pts); a mild alteration of liver function occurred in 3 patients with an increase of transaminase and bilirubin (WHO grade 1).

After chemotherapy, 15 pts (10 adenocarcinoma; 5 squamous cell carcinoma) underwent radiotherapy. Mean dose administered was 48 Gy (range 40-60). Radiotherapy produced partial improvement in four patients (26.6%) and one of them underwent surgical resec-

Table II. Hematological (% cycles) and non-hematological (% cases) toxicity after chemotherapy in 24 NSCLC pts.

Toxicity WHO grade	0	1	2	3	4
Leukopenia	18.1	25.5	35.1	18.1	3.2
Anemia	63.4	32.3	4.3	-	–
Thrombocytopenia	86	7.5	5.4	1.1	–
Nausea/vomiting	66.6	12.5	12.5	8.3	–
Stomatitis	87.5	4.2	8.3	-	–
Diarrhoea	91.7	8.3	-	-	–
Haepatic toxicity	87.5	12.5	-	-	–
Cardiac toxicity	79.2	12.5	8.3	-	–

Table III. Response rate after radiotherapy in 15 NSCLC pts pre-treated with chemotherapy.

	Pts n°	*PR (%)*	*SD (%)*	*PD (%)*
Overall	15	4 (26.67%)	7 (46.6%)	4 (26.6%)
Staging				
Stage IIIB	11	4 (36.3%)	5 (45.4%)	2(13.3%)
Stage IV	4	-	2 (50%)	2 (50%)
Histology				
Epidermoid	6	2 (33.3%)	2(33.3%)	2 (33.3%)
Adenocarcinoma	9	2 (22.2%)	5 (55.5%)	2 (22.2%)

Complete Response (CR); Partial Response (PR); Stable Disease (SD); Progressive Disease (PD).

tion; in 7pts (46.6%) there was stable disease and in 4 pts (26.6%) the condition worsened (Table III). After one year from diagnosis overall survival was 66.6% (Figure 1)

Discussion

In advanced NSCLC, the use of a poly-chemotherapy based on platinum has allowed to obtain a moderate improvement of survival compared with supportive therapy only[2]. Cisplatin-etoposide association in NSCLC has determined a median survival of about 8 months and a one-year survival for about 30% in patients in stages IIIb and IV[19-20].

In recent years, other drugs have been introduced in NSCLC therapy in an attempt to further improve survival and epirubicin is among these. Data on the efficacy of this drug in standard doses have been disappointing since an objective response was observed on average in 5% of patients[21-22]. In monotherapy it is only at high doses (105-165 mg/m^2) that epirubicin has been shown in various studies to have a good antitumoural activity with response rates between 17% and 36%[11-14] showing its potential efficacy in the treatment of NSCLC.

Using this drug at the dose of 120 mg/m^2 in association with cisplatin (60 mg/m^2), Martoni et al.[15] have obtained a partial response in 54%

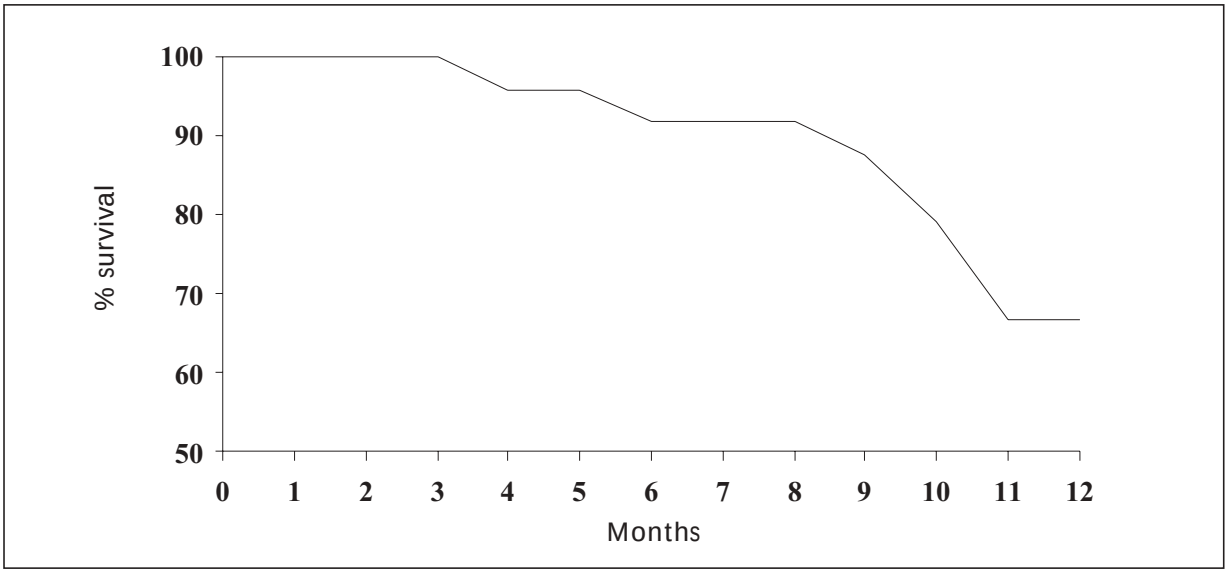

Figure 1. One-year survival curve in 24 NSCLC patients treated with combined therapy (chemotherapy and/or surgery and/or radiotherapy).

of patients and a median survival of 9 months. In a subsequent study[23] the EPI (120 mg/m^2) plus CP (60 mg/m^2) scheme was compared with the CP (60 mg/m^2) in combination with vinorelbine (25 mg/m^2 on days 1 and 8) scheme in NSCLC patients in stages IIIb and IV: no significant differences were found between these two schemes with a remission in 32% of patients treated with CP plus EPI and in 27% of those treated with CP plus VNR, median survival of 10.5 and 9.6 months and 1 year survival rate of 42% and 39% respectively.

Clerici et al.[24] administered EPI (120 mg/m^2) at a higher dose of cisplatin (100 mg/m^2) obtaining a 39% of response rate and a median survival of 10.2 months, but they also reported an high incidence of haematological toxicity with an 80% leucopoenia of grades 3-4. Also Quantin et al.[25] with a similar therapeutic scheme had a 33% of response rate and a median survival of 8 months, but also a large number of febrile neutropenia episodes. That is, by increasing dosage of platinum combined with epirubicin, median survival does not improve while toxicity gets worse.

Our study, using a high dose of EPI combined with cisplatin is in line with previous studies[15,23-26] as in the response rate improving results of reference therapeutic regimens in NSCLC therapy which include cisplatin in combination with etoposide[19-20] or with vinorelbine[27] or with gemcitabine[20]. Furthermore, a combination of EPI at high doses with CP has also shown good tolerability[24]. In our study, treatment was not stopped in all patients but rarely delayed. In regard to haematological toxicity, leukopenia was the main symptom reported, in most cases of mild or moderate grade and only in 21.3% of the cycles was it severe (< 2000/mm^3); anemia and thrombocytopenia were reported in a smaller percentage of patients and was mild to moderate. The use of growth factors (G-CSF or erithropoietin) has allowed to control these side effects easily and to administer chemotherapy according to scheduled times.

Among the non-haematological toxic effects, nausea/vomiting was found in 33.3% of cases and they were well tolerated by patients. EPI has shown transient cardiac side effects in a low number of subjects proving its good tolerability if the cumulative dose of 850 mg/m^2 is not exceeded. Some authors found a decreases in the ejection fraction of more than 10% however without finding heart failure[15,23].

The combination of drugs we have studied has shown therapeutic results similar to those obtained with other associations without worsening the patient quality of life; the administration of the two drugs on a single day per cycle simplifies patient management, reducing costs and making the treatment more acceptable for patients. The lower percentage of side effects, compared with other authors, was probably due to the extensive use of antiemetic drugs or growth factors both for white and red blood cells. Another significant element is that this therapeutic scheme can be used as neoadjuvant chemotherapy: in our study 4 patients underwent complete surgical resection of the neoplasia after restaging showed a marked regression of the tumor.

On the other hand, several studies show these results are limited and transient. Often, after short time from chemotherapy there is a flaring up of the disease which can no longer be controlled with the usual therapy. As a consequence other options capable of stabilizing or strengthening the effects of chemotherapy need to be found. Radiotherapy is used alone or in association with chemotherapy or surgery. This latter option could improve results and prognosis. So in our study the survival rate after one year from diagnosis was 66.6% with poor side-effects in accordance with other authors[28,29]. Other studies which administered chemotherapy alone and at the same doses and with the same schedule used by us report a survival of 40% after one year[23-24]. In NSCLC, combined treatment (chemotherapy and/or radiotherapy and/or surgery) in sequential modality may give better survival rates than those achievable with chemotherapy or radiotherapy alone.

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