

Gemcitabine-Cisplatin as Neoadjuvant Therapy in Locally Advanced Non-Small-Cell Lung Cancer: A Phase II Trial from Kuwait

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ABSTRACT

Purpose: The aim of this study is to evaluate the clinical efficacy and toxicity of gemcitabine plus cisplatin combination therapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer (NSCLC).

Patients and Methods: Between January 1998 and January 2000, forty previously untreated patients with stage III pathologically confirmed NSCLC were enrolled into the study. The median age of the patients was 51 years (range 33-70 years), 34 were males and 6 female patients with male to female ratio 5.6 to 1 and a World Health Organization (WHO) performance status (PS) of 0 to 2 {0 for 12 patients, 1 for 24 patients and 2 for 4 patients}.

Twenty-three patients had stage IIIA and 17 patients had stage IIIB without pleural effusion or supraclavicular lymph node metastasis. The predominant histology were squamous cell carcinoma (19 patients) adenocarcinoma (14 patients) and large cell carcinoma (7 patients). All eligible patients were allocated to receive induction chemotherapy with gemcitabine 1200 mg/m² on days 1,8 and 15 plus cisplatin 100 mg/m² (GEM-CIS) on day 15 of each 28 days cycle. Three cycles were administered followed by surgery and/or radiation therapy in the form of 60 Gys over 6 weeks to the tumor bed and regional lymph nodes. All patients have been followed for a median follow up period of 18 months (range 12-24) months.

Results: Among the 40 patients who received the GEM-CIS combination there were three complete responses (7.5%) and 23 partial responses (57.5%) for an overall response rate of 65%, 10 cases had stable disease (25%) and 4 developed progressive disease (10%). The median duration of objective response was 10.5M (8-13M) with median survival of 15.5M (10-21M). Hematologic toxicity of short duration was dose limiting with thrombocytopenia WHO grades 3 and 4 in 25% and 20% of patients respectively. Neutropenia WHO grades 3 and 4 in 17.5% and 5% of patients, respectively. Moreover 20% of the patients showed grade 3 and 4 anemia. Nausea & vomiting occurred mainly after cisplatin and were of grade 2 & 3 in 20% of the patients. Flu like symptoms (including lethargy) grade 1 & 2 were recorded in 25% of patients.

Conclusions: The GEM-CIS combination is a highly effective treatment for patients with locally advanced NSCLC with accepted level of toxicity and the 65% overall objective response appears promising and suggests that GEM-CIS is one of the most active regimens so far studied.

Key Words: Lung cancer - Non-small cell - Locally advanced - Neoadjuvant chemotherapy.

INTRODUCTION

Lung cancer is now the leading cause of cancer related death in North America and Europe for both males and females [1,2] and its incidence is likely to increase in developing countries because of the rise in tobacco consumption. Thus, it will remain a major health problem worldwide in the forthcoming decades despite the active campaigns against tobacco. Approximately 80% of the lung cancers are of the Non Small Cell subtype (NSCLC) which comprises several histologic types; squamous cell carcinoma, adenocarcinoma and large cell carcinoma. About 70% of NSCLC patients present with unresectable disease due to either locally advanced disease or dissemination. These patients are considered to be incurable with conventional treatment and are candidates for palliative radiotherapy (RT) and/or chemotherapy (CT) [3].

Even within the group of patients who were subjected to surgery, only one-third were found to be alive after 5 years. As most patients present with, or subsequently develop uncontrollable disease, the overall prognosis is poor with < 10% long term survival [4]. Traditionally, locally advanced NSCLC has been treated solely with RT. Although RT can ameliorate symptoms and

extend survival in a proportion of patients, long-term results are poor with only 5% five year survival. The limited benefit of RT is not surprising as these tumors tend to spread early in their natural history and most patients die with locoregional and systemic metastasis [5]. Although the evaluation of chemotherapy (CT) in NSCLC dated back to the early 1970s, it was only with the demonstration of the activity of cisplatin in the early 1980s that the modern era of CT investigations in NSCLC began [6].

There have been many randomized trials testing the addition of cisplatin-based combination CT to radiotherapy (CRT) [7-9]. Three of these trials have demonstrated a significant survival benefit in favor of chemotherapy [10-12]. In the Cancer And Leukemia Group B (CALGB) study, [13,14] cisplatin/vinblastin combination followed by RT was compared with RT alone, in patients presenting with excellent performance status WHO (0-1) and with no supraclavicular adenopathy. The results have been recently updated. The reported median survival, 1-year survival, and 5 years survival were as follows: 13.7 versus 9.6 months, 54% versus 40% and 19% versus 7% respectively with statistically significant difference. In the French study, [15-16] 138 patients were randomized between six courses of four-drug regimen of vindesine, lomustine, cyclophosphamide and cisplatin with RT (CRT) compared with RT alone. At a mean follow up of 61 months, patients randomized to the combined (CRT) and radiotherapy had a significant improvement in the rate of development of distant metastases and survival [15,16]. The percentage of patients alive at 1,2 and 5 years were 41%, 14% and 3% for RT and 51%, 21% and 6% for CRT, respectively. These results were in accordance with those of the recent Radiotherapy oncology group (RTOG)/European clinical oncology group (ECOG) three-arm trial comparing cisplatin /vinblastin and radiotherapy, conventional radiotherapy and hyperfractionated radiotherapy which showed that survival was superior with the combined regimen. (CRT) [17].

In an RTOG trial, [18] split course RT was compared with RT and concurrent cisplatin administered either daily or weekly. The results showed that patients who had received RT and daily cisplatin had a statistically significant improvement in survival at 3 years compared

with those who received RT alone (16% versus 2%), the development time of distant metastases was not significantly different between the two groups but the group who received daily cisplatin was found to have an improvement in survival without local recurrence.

It is not surprising that only a few studies have shown a statistically significant benefit with CRT over RT alone since 8 of the trials evaluating cisplatin-based CT randomized less than 150 patients. Meta-analysis using update patients data from multiple trials involving 3033 patients showed a statistically significant benefit for CRT compared to RT [19]. The subset of 11 trials using cisplatin-based CT provided the strongest evidence for an effect favoring CRT. The hazard ratio (HR) 0.87 corresponds to an absolute benefit of 4% at 2 years and 2% at 5 years ($p = 0.005$).

Although virtually every known cytotoxic agent has been tested for efficacy against NSCLC, historically only cisplatin, vinca-alkaloids, mitomycin-C and ifosfamide have been associated with response rate consistently > 15% [20]. After a paucity of new development in the 1980s, several new agents have entered advanced clinical investigations in the 1990s. Over the last 5 years, gemcitabine, taxoids (paclitaxel and docetaxel) and navelbine (vinorelbine) have shown single agent activity of about 20% in NSCLC. They have increased single-agent response rate, increased survival and for the most part reduced toxicity [21,22].

Of these drugs, gemcitabine was found to have a single agent response rate of 20-25% and mild toxicity making gemcitabine an attractive agent to be considered in combination regimens. Gemcitabine in combination with cisplatin was tested in several studies with promising results. The response rate and median survival reported ranged between 38 and 65% and 8.4 and 14.3 months respectively [23].

Consequently, for patients with locally advanced non metastatic unresectable stage IIIA and IIIB NSCLC we decided in this study to utilize the combination of gemcitabine/cisplatin (GC) for three-cycles to be followed by surgery and/or radical RT. The main endpoints in this study were objective response, treatment associated toxicity and overall survival.

PATIENTS AND METHODS

This work was done in Kuwait Cancer Control Center between January 1998 through January 2000.

Inclusion criteria included histologically confirmed non small lung cancer (stage IIIA and IIIB). Other criteria included: measurable disease, (WHO) PS of 0-2, age \leq 70 years, and normal organ function. No other malignancy except adequately controlled basal cell carcinoma of the skin, and no previous therapy was allowed. All patients gave informed consent.

Pretreatment evaluation included a complete history and physical examination, laboratory assessment (full blood panel, electrolytes, liver enzymes, bilirubin, creatine and creatine clearance, total protein, albumin), electrocardiogram, pulmonary function tests and tumor assessment (CAT scan of chest and upper abdomen, bone scan, and fiber-optic bronchoscopy). Other diagnostic procedures were performed according to symptoms such as CAT scan of brain.

Treatment Schedule:

Eligible patients were allocated to receive gemcitabine on days 1, 8 and 15 of every 28-days cycle. A cycle is defined as 3 consecutive weeks of treatment followed by 2 weeks rest. A dose of 1200 mg/m² of gemcitabine was administered intravenously over 30 minutes on these days of therapy. Cisplatin administered at 100 mg/m² via free-flowing intravenous line on day 15 of each 28-day cycle given after administration of gemcitabine. Patients received an IV hydration regimen and prophylactic parenteral antiemetics, consisting of a 5-HT₃ receptor antagonist plus dexamethasone, before cisplatin administration. Three cycles of neoadjuvant chemotherapy were planned followed by re-evaluation of tumour stage. In case of complete response (CR), radical radiotherapy will be given, in partial response (PR), surgery is planned and in stationary disease (SD) or progressive disease (PD) radiotherapy will be given.

Gemcitabine on day 8 and 15 was administered at a full dose only if the white blood cell (WBC) count was $> 2.5 \times 10^9/l$ and platelet count $> 75 \times 10^9/l$. Seventy-five percent of the dose was given if WBC was 1-2.5 $\times 10^9/l$ or if platelets were 50-75 $\times 10^9/l$. Before repeating a cycle, the requirements were: absolute neutro-

phil count $1.5 \times 10^9/l$, platelets $100 \times 10^9/l$, hemoglobin 9 g/dl, creatine clearance 60 ml/min, and normal liver function.

If hematologic, renal, or hepatic function did not meet these criteria, treatment was delayed until recovery for a maximum of 2 weeks. Treatment was also postponed if non-hematological toxicity grade was 3 or more.

Patients who developed sustained febrile neutropenia, WHO grade 4 thrombocytopenia or bleeding associated with thrombocytopenia were dosed at 50% of the starting dose of the previous cycle. This was applied to all cycle injections. Subsequent dose escalation to the original dose was allowed providing the patient tolerated the doses given at the 50% level

Patients went off study when treatment delays exceeded 2 weeks.

Radiotherapy Technique:

All patients received a radical dose of radiation 60 Gys, at a rate of 1.8-2 Gys/fraction 5 days a week with two-phase technique-treating the primary tumor plus regional lymph nodes with direct antero-posterior fields using linear accelerator 6-18 MV according to the patients separation up to 40 Gys at 1.8-2 Gys/fraction 5 days a week. This was followed by another 20Gys to the same treatment volume using planning technique with maximum sparing of the spinal cord.

Radical radiotherapy alone was applied for patients with complete response, stable disease or patients with progressive disease after chemotherapy and for those with partial response and labeled as medically unfit for surgery or with unresectable disease.

Surgical Treatment:

Patients who showed partial response after three cycles of GEM-CIS combination, were reassessed by chest x-ray, thoraco-abdominal C.T with contrast, spirometric pulmonary functions, ECG and full laboratory investigations. Echo cardiography and bone scan were performed when indicated.

Fourteen patients appeared operable by investigations and were explored through thoracotomy incision at the 5th intercostals space where nine patients were operable and five were inop-

erable. Lobectomy was done in five patients, two right upper, one right lower, one left upper and one left upper bilobectomy. Pneumonectomy was done in four patients, two right and two left. Hilar and mediastinal lymph node dissection was done for all cases. Extended procedures were performed in four cases, chest wall resection in two cases due to chest wall invasion and the chest wall was reconstructed by prolien mesh and bone cement, partial pericardiectomy in one case and vagus nerve sacrificed in one case. Inoperable cases were due to invasion of great vessels in three patients, invasion of trachea in one patient and invasion of oesophagus in one patient.

Postoperative pain control was achieved by thoracic epidural analgesia or intrapleural catheter analgesia. Postoperative complications occurred in four patients, atelectasis (n=2), arrhythmia (n=1) and wound infection (n=1) and there was no mortality.

Treatment Evaluation:

Response was evaluated according to South West Oncology Group (SWOG) criteria [24], at 2nd and 3rd cycles. A panel of at least three experts verified eligibility criteria, staging and toxicity and reviewed original radiological findings to evaluate response in all cases.

A complete response (CR) was defined as the complete disappearance of all objective disease. A partial response (PR) was defined as a 50% or greater decrease in the sum of the products of the two longest perpendicular diameters of all measurable lesions initially selected as a target, without progression at any other site. Stable disease was defined as less than 50% decrease or less than 25% increase in the sum of products of the two longest perpendicular diameters of all measurable lesions initially selected as a target. Progressive disease corresponded to an increase of 25% or more in the sum of products of the two longest perpendicular diameters of all measurable lesions initially selected as a target, or any new lesion not previously identified. The duration of objective responses was calculated from the start of treatment until documented disease progression in responders. Survival was defined as the interval from the date of start of treatment until the date of death or last follow-up. Toxicities were graded according to WHO criteria [25].

Comparisons between groups were done using Fisher's exact test. *p* values equal to or less than 0.05 were considered significant.

RESULTS

Between January 1998 and January 2000 a total of 40 patients presenting with stage III NSCLC were enrolled in the study. Table (1) summarizes the patients' characteristics. There were 34 males (85%) and 6 females (15%) with a male to female ratio of 5.6:1. The median age was 51 years (range 33-70 years) for the whole study group and WHO performance status of 0-2 (0 for 12 patients, 1 for 24 patients, 2 for 4 patients). Twenty-three patients (57.5%) and 17 patients (43.5%) were stage IIIA and Stage IIIB, respectively without pleural effusion or supraclavicular adenopathy. Squamous cell carcinoma was the commonest histopathological type, it accounted for 57.5%, adenocarcinoma for 35% and large cell carcinoma for 17.5%.

All 40 patients were evaluable for response and toxicity, and the efficacy data are enumerated in table (2). Following chemotherapy, three patients achieved a CR, and 23 had a PR, resulting in an overall response rate of 65%. Ten patients showed SD and 4 patients developed PD. All patients have been followed for a minimum of 12 months and a maximum of 24 months with a median follow-up period of 18 months. Fourteen out of 23 patients (60.9%) who had good partial response underwent surgical exploration, 9 out of these 14 patients (64%) had resectable disease, 5 were treated with lobectomy, 4 with pneumonectomy and the remaining 5 cases had unresectable disease.

The median duration of objective response was 10.5 months (8-13 months), and the median survival for the whole study group was 15.5 months (10-21 months).

Overall 18 deaths occurred after a median period of follow-up of 11.5 months (9-14 months).

Chemotherapy Toxicity:

The most significant toxicity was hematologic, as summarized in table (3). In 40 patients (118 cycles) thrombocytopenia, neutropenia and anemia WHO grades III and IV were encountered

in 25% and 20%, 18% and 5% and 20% of the patients, respectively. Hematologic toxicity was of short duration and required reduction in the designed doses of treatment in 12 patients (30%). Some patients needed correction with blood and platelet transfusion and colony stimulating factors. Temporary delay of treatment for one week occurred in 6 patients (15%) due to grade 4 hematologic toxicity with discontinuation of the third cycle in 2 patients (5%).

The non-hematologic toxicity is enumerated in table (4) and included nausea and vomiting that occurred mainly after cisplatin and was grade 2 in 6 patients (15%) and grade 3 in 2 patients (5%). Neurotoxicity grade 1 and 2 was encountered in 12 patients (30%) and flu like symptoms (including lethargy) in 10 patients (25%).

Alopecia grade 1 and 2 occurred in 33% and 40% of patients, respectively.

Radiotherapy Results:

Following radical radiotherapy two out of the 23 patients (8.7%) with partial response showed complete radiological response, while five patients (21.7%) showed partial response, and seven patients (30.4%) had stable disease. Minimal partial response was manifested in two out of the ten patients (20%) who had stable disease.

Acute radiation toxicity was mild (G1) oesophagitis and skin reactions predominantly in all patients. G2 reactions occurred in four patients (10%) oesophagitis. Two patients (5%) experienced G1 pneumonitis, five patients (12.5%) experienced G2 pneumonitis while only one patient had G3 pneumonitis. There were three cases of Grade 2 late lung toxicity. There was no treatment related deaths, nor cases of myelopathy.

The outcome of patients who developed pneumonitis was as follows:

- The two who developed mild pneumonitis G1 improved.

- All patients who developed moderate pneumonitis were treated with steroids, four patients (80%) improved and were no longer symptomatic. One patient had progressive pulmonary symptoms attributed to COPD. The only patient with G3 pneumonitis did not improve.

Table (1): Patient characteristics of 40 patients with locally advanced NSCLC.

Patient Characteristics	No. of Patients	%
Male	34	85
Female	6	15
Age, years median	51	
range	33-70	
Pathology		
Sq.Cell Carcinoma	19	47.5
Adenocarcinoma	14	3.5
Large cell carcinoma	7	17.5
PS		
0	12	30
1	24	60
2	4	10
Stage		
Stage IIIA	23	57.5
Stage IIIB	17	42.5

Table (2): Efficacy Response of the 40 evaluable NSCLC patients.

Objective Response	No. of Patients	%
Complete response	3	7.5
Partial response	23	57.5
Overall response	26	65
Stable disease	10	25
Progressive disease	4	10
Median duration of Response (range)	10.5 months (8-13 months)	

Table (3): Hematological toxicity after receiving chemotherapy.

Toxicity	No. of Patients	%
<i>Thrombocytopenia</i>		
G ₃	10	25
G ₄	3	20
<i>Neutropenia</i>		
G ₂	4	10
G ₃	7	17.5
G ₄	2	5
<i>Anemia</i>		
G ₂	10	25
G ₃	5	12.5
G ₄	3	7.5

Table (4): Non hematologic toxicity of chemotherapy.

Toxicity	No. of Patients	%
<i>Nausea & Vomiting</i>		
G ₂	6	15
G ₃	2	5
<i>Neurotoxicity</i>		
G ₁	9	22.5
G ₂	3	7.5
<i>Alopecia</i>		
G ₁	14	35
G ₂	16	40
<i>Flu-like symptoms</i>		
G ₁	6/40	15
G ₂	4/40	10

Table (5): Prognostic factors for response.

	Response (%)	p-value
<i>Age</i>		
<50	72.2	0.386
>50	59.0	
<i>PS (WHO)</i>		
0	83.3	< 0.002
1	62.5	
2	25.0	
<i>Stage</i>		
IIIA	73.9	0.169
IIIB	52.9	

Table (6): The relationship between surgery and survival.

	Median Survival
Resectable 9/40	17.4 months (range 15 - 21)
Unresectable 31/40	11.3 months (range 10 - 15)

DISCUSSION

Advanced NSCLC is almost a fatal disease and survival is usually measured in weeks. Long term results obtained with currently available treatment were reported to be mediocre. [16] Several randomized studies tend to favor chemotherapy over the best supportive care in advanced NSCLC [14,16,20,26], taking into consideration the quality of life and costs of treatment.

Combined chemotherapy and radiation therapy followed by surgery is considered to be the

treatment of choice for locally advanced NSCLC in medically operable patients with good performance status and in absence of weight loss [27].

Randomized trials comparing radiation therapy alone versus sequential chemotherapy cisplatin based regimen followed by radiation therapy reported the superiority of this sequential chemoradiotherapy strategy for patients with stage III NSCLC and showed significant improvement in median survival and survival at 1,2 and 3 years [10,11].

Although the best standard chemotherapy regimen for NSCLC has not been established, cisplatin based regimens were advocated. During the 1970's it was CAMP regimen (cyclophosphamide, adriamycin, methotrexate and procarbazine). More recently, vinorelbine-cisplatin, vindesine-cisplatin and ifosfamide-mitomycin - cisplatin had been successfully tested and became more popular and demonstrated higher response rate (20-31%) and less toxic than the first generation regimen. However, relative low response rate and modest survival gains from these regimens, made the discovery of more effective agents imperative [20].

Several promising new chemotherapeutic agents are currently evaluated in NSCLC such as: taxanes (paclitaxel and docetaxel), topoisomerase I inhibitors (irinotecan and topotecan), vinorelbine and gemcitabine. These new agents produced an objective response rate of 20% or more as a single agent with a median survival of 40 weeks and 1 year survival of 40% [28].

Gemcitabine (2,2, disfluorodeoxycytidine) analogue of deoxycytidine, is a novel pyrimidine antimetabolite, it is incorporated into DNA and leads to chain termination. It was developed because of its prolonged retention time in tumor cells and high rate of activity against solid tumor cells both in vitro and in vivo [29].

Three phase III randomized trials [30-32] were conducted to compare the efficacy of gemcitabine plus cisplatin combination (GC) with other chemotherapy regimens (etoposide-cisplatin, mitomycin-ifosfamide-cisplatin and cisplatin alone), in the treatment of European and North American patients with inoperable (stage IIIB or IV) NSCLC, gemcitabine-cisplatin combination yielded a statistically significant higher overall tumor response of 38%, 1 year survival of 40%

and statistically significant longer progression free interval than other chemotherapy regimens.

In the present study, we had a selected group of patients who are at higher risk of loco-regional recurrence as well as distant failure and who consequently had the lowest reported disease free survival and overall survival. Those patients were treated with the combination of gemcitabine-cisplatin (GC) to determine the clinical efficacy and toxicity of this combination. In our series the median age was 51 years, and according to our results age itself did not have any impact on response to treatment or median survival. This result cope with the results reported by Galietti et al. [31], in this retrospective study they reported that prognosis in patients under 40 years of age was similar to that in elder patients [33].

The single most important decision in evaluation of new patients with lung cancer is an overall assessment of performance status [34]. In our series most of complete response and partial response was noticed in patients with WHO performance status grade 0-1 (16.6% and 4.2% respectively for grade 0 and 66.6% and 58.3% respectively in grade 1) compared to 0% and 25% in grade 2 performance status with statistically significant difference.

Throughout the whole study 26 cases responded (65%), of them, 3 patients achieved CR (7.5%). These results are comparable to those obtained by Crino et al., [35]. In their study, 42 patients with unresectable stage III NSCLC received gemcitabine plus cisplatin as induction CT followed by surgery or radical radiotherapy and those obtained by Moorsel et al., [33] in 19 patients with stage III NSCLC treated with gemcitabine-cisplatin combination. The results were lower than that reported by Lopez et al., [36]. This may be attributed to the difference in number and patient characteristics.

In responding patients the median duration of response was 10.5 months with a range of 8-13 months throughout the whole study, with median survival of 15.5 months and a range from 10 to 23 months with better median survival 17.4 months (15-21 months) for patients who underwent surgical resection following primary chemotherapy versus 11.3 months (10-15) for those who were not operated upon.

Our results, were higher than those reported

by Sandler et al., [29], on 309 patients who were randomized between GC and cisplatin alone, in which the reported median survival for GC group was 9 months and median duration of response was 8.9 months and those reported by Le chevalier et al., [37] in a study included 192 patients with advanced NSCLC. The reported objective response and median survival were 30% and 38 weeks respectively. However our results were comparable to the results reported by Tonato, et al., [31] in phase III study included 56 patients randomized between GC combination and MIC combination, they reported overall response rate as 54% for patients treated with GC combination with median survival of 15 months and also to that reported by Einhorn et al., [38]. The difference between our data and those reported in other reports might be attributed to the fact that some studies included stage 4 cases.

In our series, hematologic toxicity was acceptable. Thrombocytopenia was the most encountered toxicity in 45% of patients, neutropenia in 23% and anemia in 20% of the patients. Notably, relatively few patients required omission (5%) or temporary delay in the treatment in 6 patients (15%). These results are comparable to those reported by the Italian lung cancer project (ILCP), [29] Spanish lung cancer group trial (SLCG) [36] and the Hoosier oncology cancer group (HOG) [38] which gave comparable response rate and toxicity using GC combination versus different cisplatin combinations, but remarkably lower than those obtained by Wozniak et al., [39] on patients with advanced and metastatic NSCLC treated with navelbine-cisplatin combination, who reported G3 and G4 neutropenia in 22% and 59%, respectively and those reported by Le chevalier et al., [37] who reported a higher incidence of neutropenia (81%) in their study that included 192 patients with advanced NSCLC treated with navelbin-cisplatin combination.

Conclusion:

The clinical results of this study provide evidence that neoadjuvant gemcitabine-cisplatin combination is a highly effective treatment for patients with locally advanced NSCLC with accepted level of toxicity, and the 65% overall objective response appears promising and suggests that GEM-CIS is one of the most active regimens so far studied. Based on the analysis of the significance of prognostic factors, we

recommend the regimen to be used in patients presenting with good performance status (0-1).

REFERENCES

- 1- Ginsberg R. J, Kris M.G. and Armstrong J.G.: Cancer of the lungs, in Devita VT Jr., Hellman S, Rosenberg SA (eds): *Cancer: Principles and Practice of oncology* (ed 4), Philadelphia, Pa, Lippincot, 1993, 673-758.
- 2- Carter D. and Eggleston J.: *Tumors of the Lower Respiratory tract*, Washington DC, Armed Forces Institute of Pathology, 1980.
- 3- Dosoretz D., Katin M. and Blitzer P.: Radiation therapy in the management of inoperable carcinoma of the lung: Results and implications for future treatment strategies. *Int J. Radiant Oncol. Biol. Phys.*, 1992, 24: 3-9.
- 4- Sause W., Kolesar P. and Taylor S.: Five year results; Phase III trial of regionally advanced unresectable non small lung cancer, RTOG 8808, EGOG 4588, SWOG 8992. *Proc Am Soc Clin Oncol.*, 1997, 118-103.
- 5- Sause W., Scott C. and Taylor S.: Radiation therapy oncology group (RTOG) 88-08 and Eastern co-operative oncology group 4588: Preliminary results of a phase III trial in regionally advanced unresectable non-small cell lung cancer. *J. Natl Cancer Inst*, 1995, 89: 198-205.
- 6- Bunn P.A.Jr.: The expanding role of cisplatin in the treatment of non-small-cell-lung cancer. *Semin Oncol.*, 1989, 16: 10-21.
- 7- Gardena Dr., Crowley J. and Livingston R.B.: Evaluation of cisplatin intensity in metastatic non-small-cell lung cancer: A phase III study of the South West Oncology Group. *J. Clin. Oncol. II*, 1993, 873-878.
- 8- Weick J.K., Crowely J. and Natale R.B.: A randomized trial of five cisplatin-containing treatment in-patients with metastatic non-small-cell lung cancer: A southwest oncology group study. *J. Clin Oncol.*, 1991, 9: 1157-1162.
- 9- Livingston R.B.: Treatment of advanced non-small lung Cancer: The southwest oncology group experience. *Semin Oncol.*, 1988, 15: 37-41.
- 10- Cullen M.H., Billingham L.J. and Woodroffe C.M.: Mitomiya, ifosfamide and cisplatin in unresectable non-small cell lung cancer: effects on survival and quality of life. *J. Clin. Oncol.*, 1999, 17: 3188-3194.
- 11- Non-small cell lung cancer Collaborative Group: Chemotherapy in non-small-cell lung cancer: A meta analysis using updated data on individual patients from 52 randomized clinical trials-non-small cell lung cancer collaborative group *BMJ*, 1995, 311: 899-909.
- 12- Wozniak A.J., Crowley J.J. and Balcerzak S.P.: Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small cell lung cancer: A southwest oncology group study. *J. Clin. Oncol.*, 1998, 16: 2459-2465.
- 13- Clamon G., Herndon J. and Cooper R.: Radiosensitisation with carboplatin for patients with unresectable stage III non-small cell lung cancer. A phase III trial of the cancer and leukemia group. *J. Clin. Oncol.*, 1999, 17: 4-11.
- 14- Dillman R.O., Herndon J. and Seagren S.I.: Improved survival in stage III non-small cell lung cancer: Seven-year follow-up of cancer and leukemia group B (CAL-GB) 8433 trial. *J. Natl Cancer Inst.*, 1996, 88: 1210-1215.
- 15- Arriagada R., Lechevalier T. and Rekeciewicz C.: Cisplatin-based chemotherapy in-patients with locally advanced non-small cell lung cancer: late analysis of a French randomized trial. *Proc Am Soc Clin Oncol.*, 1997, 16: 1601.
- 16- Lechevalier T., Arriagada R. and Quoix E.: Radiotherapy alone versus combined chemotherapy and radiotherapy in non-resectable non-small cell lung cancer: First analysis of a randomized trial in 353 patients. *J. Natl Cancer Inst.*, 1991, 83: 417-423.
- 17- Jeremic B., Shibamoto Y. and Acimovic L.: Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small cell lung cancer. *J. Clin. Oncol.*, 1995, 13: 452-458.
- 18- Lee J., Scott C. and Momaki R.: Concurrent chemoradiation therapy with cisplatin for locally advanced inoperable non-small cell lung cancer *Int. J. Radiant Oncol. Biol Phys.*, 1986, 12: 313-321.
- 19- Pisters R., Kris M. and Gralla R.: Neoadjuvant chemotherapy in locally advanced inoperable non-small cell lung cancer: metanalysis of trials comparing RT with chemoradiotherapy. In Salmon S, ed: *Adjuvant therapy of cancer*, Philadelphia, WB Saunders 1990.
- 20- Kubota K., Fwas K. and Kawahara M.: Role of radiotherapy in combined modality treatment of locally advanced non-small cell lung cancer. *J. Clin. Oncol.*, 1994, 12: 1547-1552.
- 21- Edelman M.J. and Gandara D.R.: Promising new agents in the treatment of non-small cell lung cancer. *Cancer Chemotherapharmacol*, 1996, 37: 385-393.
- 22- Lilenbaum R.C. and Green M.R.: Novel chemotherapeutic agents in the treatment of non-small cell lung cancer. *J. Clin. Oncol.*, 1993, 11: 1391-1402.
- 23- Anderson H., Lund B. and Bach F.: Single-agent activity of weekly Gemcitabin in advanced non-small cell lung cancer: A phase II study. *J. Clin Oncol.*, 1994, 12: 1821-1826.
- 24- Green S., Weiss G.R.: South West Oncology Group standard response criteria, endpoint definitions, 1992, 10: 229-253.
- 25- World Health Organization WHO handbook for reporting results of cancer treatment (WHO offset publication no. 48) Geneva, WHO, 1979.
- 26- Dillman R.O., Seagren S.L. and Propert K.J.: A randomized trial of induction chemotherapy plus radiography versus irradiation alone in stage III non small cell lung cancer. *N Eng. J. Med.*, 1990, 323: 940-945.
- 27- Gralla R.J. and Kris M.G.: Chemotherapy in non-small

- cell lung cancer: Results of recent trials. *Semin Oncol.*, 1988, 15: 2-5.
- 28- Weiden P.L. and Piartadosi S.: Preoperative chemotherapy (cisplatin + Fluorouracil) and radiation therapy in stage III non-small cell lung cancer: A phase II study of the lung cancer study group. *J. Natl Cancer Inst.*, 1991, 83: 266-272.
- 29- Sandler A., Nemunaitis J. and Dehnam C.: Phase III study of cisplatin with or without Gemcitabine in patients with advanced non-small cell lung cancer *proc Am Soc Clin Oncol.*, 1998, 17: 454.
- 30- Sandler A., Crino L. and Steward W.P.: Extended survival in stage III and IV non-small cell lung cancer (NSCLC) patients, treated with Gemcitabine plus cisplatin *proceedings of the 21st ESMO. Ann Oncol.*, 1996, 7: 91a.
- 31- Tonato M., Crino L. and Mosconi A.M.: Rational of a Phase III study comparing a standard cisplatin regimen with cisplatin and Gemcitabine in non-small cell lung cancer. *Semin Oncol.*, 1997; 24: S8-1-58-35.
- 32- Van Moorsel C.J.A., Peters G., Pinedo H.M.: Gemcitabine future prospects of single agents and combination studies *oncologist*, 1997, 2: 127-134.
- 33- Galietti F., Giorgis G. and Toffola A.: Epidemiology study of 3398 cases of lung cancer histologically ascertained in 1973 to 1984 *panminova Med.*, 1988, 30: 16-22.
- 34- Feld R., Borges M., Giner V.: Prognostic factors in non-small cell lung cancer: *Lung cancer II*, 1994, (Suppl. 3): 519-523.
- 35- Crino L., Scagliotti G. and Marangolo M.: Cisplatin-Gemcitabine combination in advanced non-small cell lung cancer: A phase II study. *J. Clin. Oncol.*, 1998, 15: 297-303.
- 36- Lopez-Cabrero M.P., Cardenal F. and Artal A.: Gemcitabine plus cisplatin versus etoposide plus cisplatin in advanced non-small lung cancer: A randomized trial by the Spanish lung Cancer group. *Lung Cancer*, 1997, 18: 10.
- 37- Le Chevalier T., Brisgand D. and Douillard J.Y.: Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small cell lung cancer: Results of European multicentre trial including 612 patients. *J. Clin. Oncol.*, 1994, 12: 360-367.
- 38- Einhorn Lit: Phase III trial of Gemcitabine plus cisplatin in non-small cell lung cancer A Hoosier Oncology Group study. *Semin Oncol.*, 1997, 24: S-28.
- 39- Wozniak A., Crowley J.J. and Balcerzak G.R.: Randomized phase III trial of cisplatin VSCDDP plus Navelbin in the treatment of advanced non-small cell lung cancer (SW) G 9308. *Proc AM SOS Clin. Oncol.*, 1996, 15: 347.