

Radiotherapy with or without Concomitant Chemotherapy as Pre- or Post-operative Therapy in Non-small Cell Lung Cancer

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Abstract

Introduction: Recently, it has been shown that in patients with unresectable non-small cell lung cancer, a short course of cisplatin and vinblastine prior to radiation significantly improves median survival and doubles the number of long-term survivors, as compared with radiation therapy alone. This combined strategy appears to produce a modest but definite improvement in unresectable lung cancer. Thus, the use of combined modality treatment in patients eligible for resection might have the ability to produce survival benefits.

Objectives: The goals are to assess the feasibility and toxicity of the combined regimen and to evaluate its ability to improve local control and quality of life by compressing the duration of treatment.

Methods: A randomized prospective pilot study using conventional radiation therapy with or without concomitant cisplatin and etoposide as an adjuvant treatment in patients who have undergone resection as well as initial therapy for those with marginally resectable disease.

Forty two patients (25 men, 17 women) participated in this study. All patients had histopathologically proven non-small cell lung cancer. Their median age was 54 years (ranged between 33 and 63 years). No one experienced loss of appetite or significant weight loss. All patients had stage II B or IIIA disease.

Group A (21 patients): Those with marginally resectable disease received two cycles of chemotherapy pre-operatively and a maximum of four cycles post-operatively. Patients with initially resectable tumors received four cycles postoperatively. Radiation therapy was begun on day 1 or 2 concomitantly with chemotherapy.

Group B (21 patients): They received radiotherapy without chemotherapy. Patients were equally distributed between both groups as regards the age, sex and tumor resectability.

Results: Group A (concomitant chemo-radiotherapy): Two patients developed marked degrees of toxicity severe enough to discontinue chemotherapy. They were shifted to the other group. The final number became 19 patients. Otherwise, the toxicity of chemotherapy was acceptable. Temporary discontinuation was necessary for fungal sinusitis in a diabetic case.

Group B: 21 patients increased to 23 after shift of these two from group A. One patient developed constrictive pericarditis, two pericardial effusions and one case had radiation pneumonitis.

Patients with initially resectable tumors underwent complete resection combined with either chemo-radiation therapy or radiation therapy alone. Eighteen out of 19 receiving cisplatin and etoposide plus radiation remain alive at the end of therapy compared with 21 out of 23 patients of group B. First year survival rates among group A and group B were 84 % (16/19) and 82 % (19/23) respectively. Third year survival rates were 78 % (15/19) and 62 % (15/23). Five year survival rates were 68 % (13/19) and 39 % (9/23) respectively, (P value = 0.001). Mean hospital stay for initial tri-modality treatment was shorter for patients in group A.

Conclusion: Concomitant chemotherapy and radiotherapy regimen is feasible and reproducible. It is more effective as adjuvant treatment in non-small cell lung cancer than radiotherapy alone.

Keywords: Chemotherapy; Radiotherapy; Concomitant chemo-radiotherapy; Bronchogenic carcinoma; Cisplatin; Etoposide

Introduction

Most patients with non-small cell lung cancer have advanced disease at the time of initial treatment and only one third of patients are candidates for curative lung resection.

Treatment of advanced lung cancer has evolved from trials of postoperative adjuvant radiotherapy to postoperative chemotherapy to induction chemotherapy and induction chemo-radiotherapy [1].

In recent years, there has been increasing evidence that the use of concomitant chemotherapy and radiotherapy is feasible in the treatment of non-small cell lung cancer.

Recently, it has been shown that even in patients with unresectable stage III, a short course of cisplatin and vinblastine prior to radiation

significantly improved median survival and doubled the number of long-term survivors, as compared with radiation therapy alone [2].

Our hypothesis was that tri modality therapy for lung cancer will

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be reproducible and prolong symptom-free interval among patients with early cases of non-small cell lung cancer with a rate of toxicity and morbidity lower than the bimodality therapy (without chemotherapy).

Objective and Rationale

Current study represents the results of a randomized prospective pilot study using conventional radiation therapy with or without concomitant cisplatin and etoposide as an adjuvant treatment in patients who had undergone resection as well as initial therapy for those with marginally resectable disease. Cisplatin is a well-known and extensively studied radiation sensitizer. The combination of cisplatin and etoposide has clear synergistic effects against a variety of human tumors and can produce a response rate of 30–40% in patients with non-small cell lung cancer [3]. The Eastern Cooperative Oncology Group reported that patients randomized to this combination had a modest but increased survival over patients treated with the other drug regimens [4].

The goals are to assess the feasibility and toxicity of the combined chemo-radiotherapy regimen and to evaluate its ability to improve local control and quality of life by shortening the duration of treatment.

Methods

This randomized prospective pilot study included 42 patients. 25 men and 17 women participated in this study. We received these patients at the Department of Chest Surgery- Suez Canal University Hospitals and Ben Sena Teaching Hospital-Yemen during the period from 1st Mar 2005 through 29th Feb 2008. Follow up continued for sixty months. Consent from patients and approval of The Ethics Committee were obtained.

All patients had not experienced neither decrease of appetite nor weight loss. Staging evaluation included bronchoscopy, bone scan, CT-scan of the chest, upper abdomen and brain. Invasive staging of mediastinal lymph nodes was performed as indicated by CT-scan. We used mediastinoscopy or mediastinotomy to biopsy lymph nodes having 1.5 cm or more in shortest diameter in stations 1 to 9. All had histological diagnosis of non- small cell lung cancer. Their median age was 54 years (range: 33-63 years). Patients had stage IIB or IIIA disease. They were randomized to receive radiation or chemo-radiation therapy.

Patients with marginally resectable disease were randomized to receive radiation or chemo-radiation before possible surgery. They received two cycles of chemotherapy pre-operatively and a maximum of four cycles post-operatively. Patients with initially resectable tumors were randomized to receive four cycles of chemotherapy or radiotherapy postoperatively.

Radiation therapy was begun on day 1 or 2 concomitantly with chemotherapy or was given alone. Two patients discontinued chemotherapy and were added to group B. Initially Group A, included 21 patients after this shift, they became reduced to 19 patients. Group B: became 23 patients who received radiotherapy without chemotherapy. Patient characteristics are listed in Table 1.

All patients underwent pulmonary resection and had complete lymph node dissection. The latter was guided by computerized tomography of the chest and results of mediastinoscopy.

Chemotherapy, when given, consisted of cisplatin 60 mg/m² square on day 1 and etoposide 100 mg/m² square on day 1,2 and 3 repeated at 21–28 day intervals, based on recovery of white blood count to a minimum of 4,000/c mm and platelet count of 100,000/c

| | Chemo-radiation (group A) | Radiation (group B) |
|--------------------------------|---------------------------|---------------------|
| Final Number of patients | 19 | 23 |
| Median age in years | 52 | 53 |
| Male patients | 11 | 14 |
| Female patients | 8 | 9 |
| Histological types: | | |
| Adenocarcinoma | 12 | 14 |
| Squamous cell | 6 | 7 |
| Large cell | 1 | 2 |
| Stage: | | |
| IIB (T2 N1M0) | 5 | 5 |
| IIIA (T1N2M0) | 3 | 4 |
| (T2N2M0) | 4 | 5 |
| (T3N0M0) | 5 | 6 |
| (T3N1M0) | 1 | 2 |
| (T3N2M0) | 1 | 1 |
| Pulmonary resection: | | |
| Lobectomy | 7 | 9 |
| Bilobectomy | 6 | 8 |
| Pneumonectomy | 4 | 4 |
| Wedge resection (biopsy alone) | 2 | 2 |
| Mean hospital stay in days | 9 ± 2.1 | 11 ± 1.6 |

Table 1: Characteristics of patients.

mm. Preventive use of G-CSF (granulocyte colony-stimulating factor) or GM-CSF (granulocyte macrophage colony-stimulating factor) was applied according to the guide lines described by the American Society of Clinical Oncology [5]. Updated guidelines for anti-emetics in oncology were applied [6]. Radiation therapy was given to both groups of patients A and B, on day 1 or 2 concomitantly with chemotherapy or given alone. Treatment consisted of thirty-three 180 cGy fractions (total dose, 5940 cGy) for patients receiving radiation alone in group B.

For those in group A, undergoing concomitant chemo-radiotherapy 30 fractions were given (5400 cGy total). Treatment was withheld if white blood cell counts were lower than 2000/c mm or platelet levels were below 50,000/c mm. Individualized treatment planning employs lead shielding tailored to shape the field and limit the radiation exposure of normal tissues. Often the radiation is delivered from two or three different positions. Conformal three-dimensional treatment planning permits the delivery of calculated doses of radiation to the target mass without increasing complications in the transit volume.

Despite the small number of patients, the two groups were well matched for age, histological type and stage of tumor.

Statistical Analysis

The sample size was calculated according to Gay's equation: (multiplying thirty by number of variables Gay, 1980) and according to Freund & Wilson equation. The variable is trimodality therapy versus bimodality therapy. The average flow of non-small cell lung cancer to our center is 1 to 2 cases per month, according to previous studies 5-year survival rate is about 14 to 20% The accepted error 10%, The Sample size according to Freund & Wilson's equation = $(1.96 / 0.10)^2 (20) (70) = 30$. According to Gays = $30 \times 1 = 30$. As some patients may be lost or become unable to complete the follow up, the study included 42 patients.

We used the mean, the percentage and the median values. SPSS program was used to apply bivariate analysis for correlation between method of treatment and survival on one side and modality of treatment

and toxicity on the other side. Kaplan-Meier curves for survival were added (Figure 1).

Results

The toxicity of chemotherapy was acceptable, early discontinuation was indicated in two patients due to an anaphylactoid reaction, *candida esophagitis*, cardiac arrhythmia and patient refusal. Temporary discontinuation was necessary for fungal sinusitis in a diabetic patient who completed the therapy after a short time. Esophagitis and radiation pneumonitis required steroid therapy. Eighteen out of 19 patients who received cisplatinum and etoposide plus radiation were alive by the end of the therapy. They recorded a five-year survival rate of 68%. Those who received adjuvant radiation, 21 out of 23 patients were alive by the end of therapy. One patient developed constrictive pericarditis and early pericardectomy was done. Two patients developed recurrent, rapidly accumulating pericardial effusion. Malignant cells were not detected in any one of these effusions. Thoracoscopic pericardial window was performed for each one. Another one developed Radiation pneumonitis.

They recorded 5-year survival rate of 39 %. The difference in survival rate between group A and group B was statistically significant. (p value = 0.001).

The rate of toxicity was generally low but severer among patients who had chemo-radio therapy; the difference was statistically insignificant, Mean hospital stay was 9 ± 2.1 days for patients in group A while it was 11 ± 1.6 days among patients in group B (Table 2).

Discussion

Lung cancer remains the most common cause of death by malignancy in both men and women. Two thirds of the cases are resectable at presentation but resection is not curable in most of them. The diversity of molecular abnormalities in non-small cell lung cancer

| Patients | Group A | Group B |
|---|---------|---------|
| No. | 21 | 21 |
| No. after severe toxicity of chemotherapy | 19 | 23 |
| Survivors at the end of therapy | 18 | 21 |
| Mortality during therapy | 1 (5%) | 2 (8%) |
| Five-year survival | 68% | 39% |
| Toxicity of therapy: | | |
| - Anaphylactoid reaction, candida esophagitis, cardiac arrhythmia | Two | Zero |
| - Bone marrow depression | One | Zero |
| - Constrictive pericarditis | Zero | One |
| - Pericardial effusions | Zero | Two |
| - Pneumonitis | Zero | One |

Table 2: The results.

may partly contribute to variable results of therapy. Also, adjustments in dosage of chemo-therapeutic agents or changes in radiotherapy planning could reduce toxicity and improve results [7].

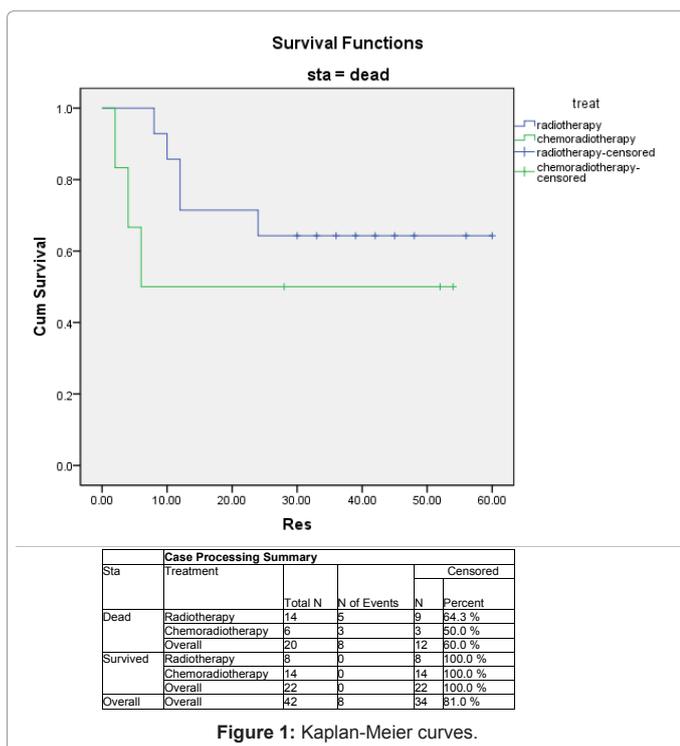
Radiation therapy (Teletherapy) is a component of curative therapy for a number of diseases, including breast cancer, Hodgkin's disease, head and neck cancer, prostate cancer and gynecological cancers. Radiation therapy can also, palliate disease symptoms in a variety of settings: relief of bone pain from metastatic disease, control of brain metastases, reversal of spinal cord compression and obstruction of superior vena cava, shrinkage of painful masses and opening of threatened airways [8]. Acute toxicities include skin erythema and ulceration and bone marrow suppression. These were alleviated among our patients by interruption of treatment. Chronic toxicities included pericardial effusions, chronic constrictive pericarditis and lung fibrosis interfering with efficiency of cardiac and pulmonary functions. They were minimized by proper planning of the radiotherapy. Recurrent rapidly accumulating pericardial effusion indicated pericardial window in two cases. Constrictive pericarditis indicated pericardectomy in one case.

Cisplatin was discovered fortuitously by observing that bacteria present in electrolysis solutions could not divide. Only the cis-diamine configuration is active as an antitumor agent. Cisplatin requires administration with adequate hydration, including forced diuresis with mannitol to minimize renal damage. In conventional doses, hearing loss is likely to develop in 50% of patients. Etoposide is one of the antitumor antibiotics. Toxic effects include myelosuppression, nausea and transient hypotension related to the speed of administration [9].

Indications for the clinical use of G-CSF (granulocyte colony-stimulating factor) & GM-CSF (granulocyte macrophage colony-stimulating factor) are both preventive and therapeutic. According to the American Society of Clinical Oncology preventive uses include:

1- With the 1st cycle of chemotherapy (primary colony-stimulating factor administration).

- If the probability of febrile neutropenia is $\geq 20\%$.
- If the patient is having neutropenia or active infection.
- Age is above 65, treated for lymphoma or other tumors, with curative intent.



- Poor performance status.
- Extensive prior chemotherapy.
- Dose dense therapy.

2-With subsequent cycles if febrile neutropenia has previously occurred.

Anemia associated with chemotherapy can be managed by transfusion of packed red blood cells. Transfusion is not undertaken until the hemoglobin falls to < 80 gm/L (8 gm/dL).

Current randomized prospective pilot study was designed to explore the feasibility of reproducing a regimen for delivering concomitant chemo-radiation using moderate dosage cisplatin on day 1 plus etoposide on days 1,2 and 3 in 21-28 day cycles with a goal of 4 cycles of treatment along with radiotherapy. There are several theoretical reasons why a simultaneous approach would be advantageous. First, a situation where there are local recurrences and systematic metastases, there is the early delivery of each treatment modality- each with its independent activity. In the post-operative sitting, each treatment can be initiated within 6 weeks of surgery. This eliminates the concern that chemoradio-therapy administered before radiation might produce an unwelcome delay that could compromise local control or even produce resistance of the tumor cell to radiation. On the other hand, one of the arguments in favor of induction or neo-adjuvant chemotherapy is that initial radiation may alter tumor blood flow or decrease patient tolerance or sensitivity to chemotherapy [10,11]. Second, the toxicity profiles of the two modalities are sufficiently different to allow high doses of each in order not to compromise the effects of either. The toxicity of radiation is for the most part limited to the mediastinum and lungs. The side effects of chemotherapy often involve the bone marrow, the kidney and liver. Finally, cisplatin and radiation have synergistic cyto-toxicity. Cisplatin can generate free radicals that will enhance radiation and can inhibit repair of the damage caused by radiation, specially damage induced on DNA, RNA and protein cross-links. Enhanced survival with concomitant chemo-radiotherapy has been shown for patients treated in randomized studies for renal, pancreatic, colorectal, small cell lung, head and neck and cancer cervix. This is presumed to be due to improving local and systemic control, a decrease in radio-resistance and elimination of sites of early metastases [12] (Table 3).

Caution is required in drawing any conclusions regarding survival given the small size of our group of patients. Current study showed that the combined chemo-radiotherapy regimen proved its feasibility and reproducibility. It has the ability to improve local control and quality of life by shortening the duration of treatment.

| Survival | Group A (tri modality therapy) | Group B (bi modality therapy) no chemotherapy | P value |
|------------------------|--------------------------------|---|---------|
| After start of therapy | 19 (100%) | 23 (100%) | |
| By the end of therapy | 18 (95%) | 21 (91%) | |
| 1 st year | 16 (84%) | 19 (82%) | |
| 2 nd year | 16 (84%) | 18 (77%) | |
| 3 rd year | 15 (78%) | 15 (62%) | |
| 4 th year | 15 (78%) | 11 (44%) | |
| 5 th year | 13 (68%) | 9 (39%) | |
| 5-year survival rate | 68% | 39% | 0.001 |

Table 3: Survival among both groups.

Conclusions

Concomitant cisplatin, etoposide and radiation therapy regimen is feasible and reproducible. It is more effective as adjuvant treatment in non-small cell lung cancer than postoperative radiotherapy alone.

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