High Dose Tamoxifen plus Cisplatin and Etoposide in the Treatment of Patients with Advanced, Inoperable Nonsmall Cell Lung Carcinoma

Chih-Hsin Yang, M.D.[1,2]
Ann-Lii Cheng, M.D., Ph.D.[1,3]
Kun-Huei Yeh, M.D., Ph.D.[1]
Chong-Jen Yu, M.D., Ph.D.[3]
Jing-Fang Lin, R.N.[1]
Pan-Chyr Yang, M.D., Ph.D.[2,3]

[1] Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan.

[2] Graduate Institute of Medicine, National Taiwan University, Taipei, Taiwan.

[3] Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.

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Address for reprints: Pan-Chyr Yang, M.D., Ph.D., Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan.

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BACKGROUND. Tamoxifen sensitizes cancer cells to chemotherapeutic agents. High dose tamoxifen has been tested in the treatment of patients with melanoma and other cancers. The authors conducted a Phase II study of high dose tamoxifen plus cisplatin and etoposide for patients with advanced, inoperable nonsmall cell lung carcinoma.

METHODS. Patients with Stage IIIB, Stage IV, or recurrent disease; good performance status; measurable lesions; and good organ function were eligible. Tamoxifen 150 mg/m^2/day, divided into 4 doses, was given for 8 days. Cisplatin 60 mg/m^2 was given on Day 4. Etoposide 60 mg/m^2/day was given on Days 4–8. Patients were allowed to remain in the study until either intolerable toxicity was observed or disease progression occurred.

RESULTS. Forty patients were accrued and received a total of 191 cycles of treatment. All patients were evaluable for response and toxicity. One patient had a complete remission and 14 had a partial remission (overall response rate, 37.5%). The median survival was 47 weeks. One-year survival was 44%. Increased thrombotic episodes were noted; all were clinically manageable.

CONCLUSIONS. High dose tamoxifen can be administered safely in combination with cisplatin and etoposide to patients with advanced nonsmall cell lung carcinoma. Favorable response rates and survival times were obtained. The value of high dose tamoxifen in the treatment of patients with nonsmall cell lung carcinoma can be evaluated further in randomized Phase III studies. ***Cancer* 1999;86: 415–20.** © *1999 American Cancer Society.*

KEYWORDS: tamoxifen, cisplatin, etoposide, nonsmall cell lung carcinoma.

Combination chemotherapy may provide symptom palliation and possible life prolongation for patients with nonsmall cell lung carcinoma (NSCLC) who are not candidates for curative surgery or radiotherapy. A cisplatin-containing regimen has been recommended as standard treatment for these patients.[1]

Despite the improvement of chemotherapy in advanced NSCLC, better treatments to improve response and survival rates still are needed. One strategy to improve treatment for patients with advanced carcinoma is to use new anticancer agents. An alternative approach is to use relatively nontoxic agents to increase the chemosensitivity of cancer cells.

Tamoxifen is a nonsteroidal, antiestrogen drug. It has been used widely in the treatment of breast carcinoma. Tamoxifen exerts its effect through the inhibition of estrogen receptor-mediated cell growth. Apart from its usual therapeutic application, tamoxifen was tested in other estrogen receptor negative cancers. Oral administra-

tion of high dose tamoxifen may result in a plasma concentration between 2 μM and 7 μM.[2–4] Tissue concentrations of tamoxifen and its major active metabolites N-desmethyltamoxifen may be even higher.[5] Tamoxifen in this concentration range is biologically active in vitro. Ramu et al. showed that 3.0 μM tamoxifen may reverse acquired resistance to doxorubicin in p-glycoprotein-expressing mouse leukemic P388 cells.[6] In addition, a synergistic reaction between tamoxifen and cisplatin has been demonstrated in several types of cancer.[7,8] Tamoxifen has been shown to sensitize cancer cells to chemotherapeutic agents. We have demonstrated previously that 5 μM tamoxifen sensitized p-glycoprotein negative bladder carcinoma cell lines to several chemotherapeutic agents.[9] Three micromolars of tamoxifen may sensitize NSCLC cancer cells to cisplatin, etoposide, and paclitaxel in vitro (unpublished observation).

High dose tamoxifen was introduced first by Del Prete et al. in advanced melanoma patients.[10] It also was tested in patients within acute leukemia,[4] ovarian carcinoma,[11] hepatocellular carcinoma,[12] and glioma.[13] There is no report of high dose tamoxifen in the treatment of NSCLC patients.

One large cell lung carcinoma patient attained partial remission for 4.5 months after treatment with cisplatin and etoposide plus high dose tamoxifen (PET regimen) after the failure of a cisplatin and etoposide combination treatment.[14] Encouraged by this observation, we started a Phase II trial to test whether high dose tamoxifen can be administered safely to patients with advanced NSCLC and whether this regimen may result in favorable response rates and survival times.

MATERIALS AND METHODS

Patient Eligibility

Patients with histologically or cytologically confirmed NSCLC were eligible for this study. They were required to have Stage IIIB, Stage IV, or recurrent disease and could not be candidates for curative surgery or radiotherapy. Any patients with brain metastasis were excluded from the study. Patients had to be age >18 years and had to have a Karnofsky performance status $\geq 60\%$. No prior chemotherapy or any other concurrent cancer treatments were allowed. There had to be measurable lesions either by physical examination or radiography. Patients were required to have good organ function (white blood cells [WBC] $\geq 4000/mm^3$, platelet $\geq 100{,}000/mm^3$, creatinine < 2.0mg/dL, bilirubin < 3mg/dL). Patients included on the study could have no prior history of thromboembolism and no serious concomitant medical conditions. Patients were required to sign informed consent to enter the study. The American Joint Committee on Cancer/International Union Against Cancer staging system for lung carcinoma was used in this study.[15]

Treatment Plans

Patients were treated with oral tamoxifen 150 mg/m^2 per day divided into four doses for 8 consecutive days. Cisplatin 60 mg/m^2 intravenous infusion for more than 1 hour was given on Day 4. Etoposide 60 mg/m^2/day intravenous infusion for more than 1 hour per day was given on Days 4–8 for a total of 5 days. Cycles were repeated every 3–4 weeks as soon as WBC counts became $>3500/mm^3$ and platelet counts became $>100{,}000/mm^3$. Dose modification was provided at subsequent cycles to reduce cisplatin and etoposide doses to 75% or 50% of the original dose if Grade 4 leukopenia was documented at the nadir of the previous cycle. Tamoxifen was discontinued if there was any evidence of thromboembolism confirmed by duplex echography, venography, or phlethysmography. Patients could be retreated with high dose tamoxifen after recovery from thromboembolic episode.

Response and Toxicity Assessment

Tumor evaluations were done at the end of every two cycles. The World Health Organization criteria for tumor response were used as criteria for partial response, complete response, stable disease, and disease progression. Toxicity assessments were performed at the end of every cycle according to the Eastern Cooperative Oncology Group (ECOG) criteria. Patients were removed from the study if they had disease progression. For stable or responding patients, treatment continued until disease progression, until no further tumor shrinkage after Cycle 6, or until unacceptable toxicity developed.

Statistical Considerations

Overall survival is defined as the period from the date of enrollment until the time of death. Progression free survival is defined as the time from the date of enrollment until disease progression. Response duration is defined as the period from the date of enrollment until responding patients experience disease progression. The 95% confidence interval is used to estimate true response rates. Kaplan–Meier analysis was used to measure median survival, median progression free survival, and 1-year survival. Ninety-five percent confidence intervals of survival data are given where indicated.

RESULTS

Patients Characteristics

Forty patients (24 men and 16 women) met the criteria and were accrued to this Phase II study. All patients signed informed consent before entering the study.

TABLE 1
Characteristics of 40 Patients with Advanced Nonsmall Cell Lung Carcinoma

Characteristic	No. of patients
Age in yrs (median)	37–78 (61)
Karnofsky performance status	
100	1
90	11
80	18
70	7
60	3
Histology	
Squamous carcinoma	11
Adenocarcinoma	27
Adenosquamous carcinoma	1
Large cell	1
Clinical stage	
IIIB	12
IV	21
Recurrence	7
Sites of involvement	
Lung	40
Pleural effusion	7
Lymph nodes	24
Liver	3
Bone	10
Adrenal glands	4
Skin	1
No. of sites	
1	5
2	15
3	16
4	4
Prior treatment (no. of patients)	
Surgery	6
Radiotherapy	7

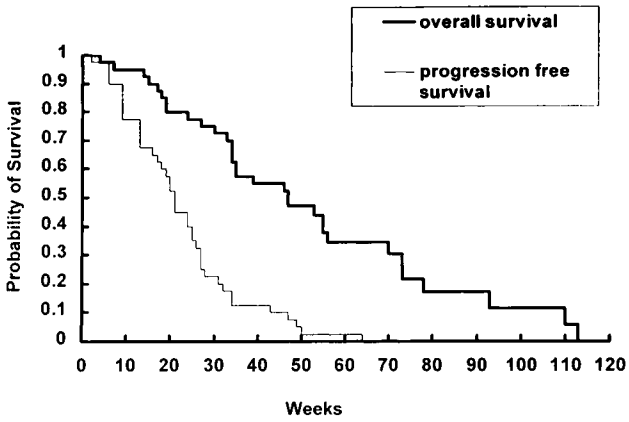

FIGURE 1. Overall survival and progression free survival of 40 patients with nonsmall cell lung carcinoma who were treated with cisplatin and etoposide plus high dose tamoxifen (PET regimen).

TABLE 2
Severe (Grade 3–4) Treatment-Related Toxicity in 40 Patients

Toxicity	No. of patients	%
Leukopenia	16	40.0
Thrombocytopenia	12	30.0
Infection	1	2.5
Febrile neutropenia	4	10.0
Nausea/vomiting	9	22.5
Stomatitis	2	5.0
Liver toxicity	1	2.5
Deep vein thrombosis	4	10.0
Cerebral thrombosis	1	2.5
Ototoxicity	5	12.5

Demographic data are shown in Table 1. Twelve patients had Stage IIIB disease at the time of enrollment; none of them were candidates for definitive radiotherapy or surgery. All 40 patients were chemotherapy naïve.

Treatment Cycles and Dosage

At the time of analysis, all patients had finished their treatment. Forty patients completed a total of 191 cycles of treatments: Each received 1–11 cycles of treatment (median, 5 cycles). One patient received only 1 cycle of treatment. Dose modifications were required in 4 patients due to Grade 4 leukopenia (WBC $< 1000/mm^3$) in previous cycles. One patient had skipped a few doses of tamoxifen because of severe vomiting.

Treatment Efficacy

One patient had a complete response, 14 patients had a partial response, and the overall response rate was 37.5% (95% confidence interval, 22.5–52.5%). Twenty-one patients had their disease stabilized, and 4 patients had disease progression. The median response duration of the 15 responding patients was 27 weeks (95% confidence interval, 17–38 weeks). The overall median survival for all 40 patients estimated by Kaplan–Meier analysis was 47 weeks (95% confidence interval, 27–67 weeks). The median progression free survival for all 40 patients was 21weeks (95% confidence interval, 19–24 weeks). The 1-year survival rate was 44% (Fig. 1).

Toxicity Assessment

Treatment-related toxicities are tabulated in Table 2. Leukopenia was the most frequent toxicity; however, Grade 4 leukopenia occurred in only 6 patients. Infections occurred in 13 patients. Febrile neutropenia occurred in only 4 patients. Nausea and vomiting occurred in almost all patients; however, only 9 patients had Grade 3 or 4 vomiting. Two patients had Grade 3 stomatitis. Four patients had deep vein thrombosis

and required hospitalization and heparinization. One patient with hypertension and diabetes developed cerebral thrombosis and was taken off the study; the patient then received cisplatin with etoposide but without tamoxifen. Only one patient died of treatment-related toxicity (infection).

Follow-up Treatments and Cause of Death

Thirty-one patients died: 29 of progressive disease, one of treatment-related toxicity (infection), and one of change in mental status. The latter patient experienced progressive disorientation and changes in mental status after five cycles of treatment. Magnetic resonance imaging revealed hydrocephalus and periventricular gadolinium enhancement. Meningeal metastasis was suspected, but there was no cytologic evidence. A ventricular peritoneal shunt was performed. This treatment resulted in only transient recovery of his mental status, and he died 5 months after the onset of neurologic deterioration.

The reasons for discontinuing treatment in 40 patients included progressive disease in 24 patients, toxicity of the treatment in 6 patients (1 vomiting, 1 cerebral thrombosis, 1 deep vein thrombosis, 1 infection, 2 poor performance and general weakness), change in mental status in 1 patient, stable disease after 6 cycles in 7 patients, and refusal of further treatment by 2 patients. Fifteen patients received second-line chemotherapy at the time of disease progression (7 with a paclitaxel-based regimen; 5 with mitomycin, vinblastine, and cisplatin; and 3 with other regimens).

DISCUSSION

Combination chemotherapy is not curative, but it offers symptomatic relief and possible prolongation of life for patients with inoperable Stage IIIB, Stage IV, or recurrent NSCLC.[1] However, the survival advantages for patients with NSCLC treated with chemotherapy are small. Better regimens are needed.

Drug resistance is the major obstacle in cancer chemotherapy. Reversal of resistance can be used as a strategy to increase efficacy of chemotherapy in cancer patients. Several clinically available compounds have been shown to reverse drug resistance in vitro and have now been tested in clinical trials, including tamoxifen. Tamoxifen has been shown to enhance the cytotoxicity of etoposide, cisplatin, and other chemotherapeutic agents in melanoma, ovarian carcinoma, and bladder carcinoma cells.[8,9,16,17] High dose tamoxifen, per se, may be cytotoxic to cancer cells. Tamoxifen at 10 μM may inhibit protein kinase C,[18] induce the expression of transforming growth factor-β,[19] and inhibit insulin-like growth factors.[20] The presence of estrogen receptors in some NSCLC cells may account for the toxic effect of tamoxifen on cancer cells.[21]

High dose tamoxifen has been tested in several types of cancer patients. Del Prete et al. first indicated that tamoxifen may enhance chemosensitivity in advanced carcinoma.[10] McClay et al. subsequently showed that deletion of tamoxifen may result in a decrease of response rate in melanoma patients.[21] The result of a randomized study in melanoma showed a trend toward beneficial effects of adding high dose tamoxifen in combination chemotherapy. However, the conclusion of that study indicated that addition of high dose tamoxifen does not increase response rates or survival times compared with chemotherapy alone.[22] None of the studies has yet shown a definitively additive effect of tamoxifen to chemotherapy.

Longeval and Klastersky used cisplatin and etoposide in 94 patients with advanced NSCLC: A 38% response rate and a median survival of 7.5 months were noted.[23] The accumulated response rate of cisplatin and etoposide in 647 patients from 7 trials was 28% (20–30%).[24–30] The median survival times in these 7 studies ranged from 24.5 weeks to 32 weeks. This combination resulted in the highest 1-year survival rate (25%) among all combination chemotherapy studies of advanced NSCLC in the ECOG.[31] A recent ECOG randomized Phase II study using cisplatin and etoposide as control arm in patients with NSCLC showed a 16% response rate and a median survival of 37.9 weeks.[32] We have observed a response rate of 37.5%, a median overall survival of 47 weeks, and 1-year survival of 44% in this study, exceeding the outcomes reported in most of the earlier cisplatin and etoposide combinations trials in NSCLC.

Reports of toxicities related to high dose tamoxifen have been few. Trump et al. observed dose-limiting neurotoxicity, including grand mal seizure, tremor, hyperreflexia, unsteady gait, and dizziness, in $>$50% of patients treated with tamoxifen ($>$150 mg/m^2 twice a day) in combination with vinblastine.[2] Reversible neurotoxicity has been described in other studies.[16] On the other hand, there were no occurrences of neurotoxicity in 4 leukemic patients treated with 700 mg/day of tamoxifen.[4] Neurotoxicity was rare in other studies that used a tamoxifen dose $<$480 mg/day.[3] We have not observed any of the neurotoxic effects, such as seizure and unsteady gait, described by Trump et al.[2]

There are conflicting reports of coagulation problems in the patients treated with high dose tamoxifen. A higher incidence of deep vein thrombosis has been reported in some studies,[3,16,21] whereas others did not report any thrombotic episodes.[2,33] There was no increased incidence of thromboembolism in melanoma

patients randomized to the high dose tamoxifen arm in one randomized, double-blind, controlled study.[22] We have experienced five episodes of thrombosis. Only two patients could not continue treatment because of this side effect. Although we seem to encounter a higher incidence of thromboembolic episodes in this study, all episodes were clinically manageable. Other toxicities observed in our study were very similar to those observed for the cisplatin and etoposide combination.

In summary, favorable response rates and survival times were found in 40 patients with NSCLC who were treated with PET chemotherapy. Apart from clinically manageable thrombotic episodes, toxicities of the PET regimen were similar to those of the cisplatin and etoposide combination. PET is a safe and effective regimen for the treatment of patients with NSCLC. This is the first series of patients to show that high dose tamoxifen may be useful in the treatment of NSCLC. The response rates and survival times of this combination are similar to what can be reached with new drug combinations, such as paclitaxel and cisplatin. Adding high dose tamoxifen to one of the new drug combinations is another interesting approach. However, a large, randomized study is the only way to determine the effectiveness of high dose tamoxifen as a chemotherapy-sensitizing agent for patients with NSCLC.

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