

**A Pilot Study in Combination Docetaxel and
Oxaliplatin with Weekly Chemotherapy
Regimen in Non-Small Cell Lung Cancer**

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1. Introduction :

Cancer is one of the most lethal reasons of human being, and became an important health issue in world widely. Clinical treatment schedules including surgery, chemotherapy, radiotherapy, and combination several of them. Although surgical resection could cure some kinds of neoplasm especially in early stage, however most kinds of cancer still needs chemotherapy or radiotherapy for advanced treatment. For the treatment objective, chemotherapy could be distinguished to neoadjuvant, adjuvant and palliative regimen. Several chemotherapy agents were approved in more than one indication, and combination chemotherapy were became a trend in cancer therapy.¹⁻³

Lung cancer was a common neoplasm in oncology, and there are two major categories of them, one is small cell lung cancer, and the other is non-small cell lung cancer. Most kinds of lung cancers are non-small cell cancers, which are our interesting in this study. Several chemotherapy regimens were building by many clinical trials, such as taxanes-based, platinum-based, and other new target therapy.⁴⁻⁷

Docetaxel is a semi-synthetic taxoid derived from baccatin II, which is obtained from the needles of the European yew tree. Since several phase III clinical trials for supporting the clinical benefit about survival and tumor responses, docetaxel was became the first line and second line chemotherapy with/without cisplatin in non-small cell lung cancer.^{6,8,9} Several treatment schedules were found out such as weekly, biweekly,

three weeks, and monthly. Although docetaxel could support good tumor responses rate and survival benefit in non-small cell lung cancer, but the hematological side effect especially in grade 3 to 4 neutropenia still be the major concern about dose-limited toxicity. Weekly docetaxel is an effort to reduce toxicity and has been identified as a safe and effective regimen in clinical trials, and fatigue became the common adverse.¹⁰

Platinum classification agents such as cisplatin, carboplatin, and oxaliplatin also showed the activity in differential tumor cell lines, and became the platinum-base regimen in chemotherapy in several kinds of neoplasm.^{4,11} Oxaliplatin is third generation of platinum compound, and the mechanism of antineoplastic activity is inhibiting DNA synthesis by causing intrastrand cross-link in DNA.¹² Oxaliplatin was approved by FDA since 2002 August, and most popular regimen is infusion leucovorin and 5-fluorouracil (FOLFOX4) for metastatic colorectal carcinoma. Clinical evidences supported oxaliplatin with high tumor response rate and prolong progression free survival in colorectal cancer, and without cross-resistance to other platinum agents in other neoplasm. The major toxicity of oxaliplatin is neuropathy, and due to cumulative dose more than 800 mg treatment, and could be reversed by stop treatment. There were several randomized studies for control neurotoxicity, such with glutathione, vitamin E, and psychiatric agents. Weekly oxaliplatin also be treated on colorectal neoplasm with good tolerance, and efficacy.¹³

In 2000-2005 American Society of Clinical Oncology Meetings,

there were differential regimens studies in breast cancer, gastric cancer, non-small cell lung cancer, and ovarian cancer.^{14,15} Based on the results, docetaxel 75 mg/m² on day 1 and oxaliplatin 100 mg/m² on day 2 in 3 weeks schedule should safety dose and with tumor response. However, there was no any regimen about weekly docetaxel with oxaliplatin combination therapy.

In a phase II study, when new antifolic chemotherapy agent pemetrexed with vitamin B12 and folic acid nutritive support could decrease hematological effect.^{16,17} In clinical practices, oxaliplatin usually be used with 5-fluourouracil and leucovorin in colorectal cancer than monotherapy. Leucovorin is the active form of the B complex vitamin, and folate composes, and like to pemetrexed nutritive supportive agents. Vitamin E could reduce neurological adverse, and protect platinum induced neuropathy.¹⁸⁻²⁰

Weekly combination chemotherapy with docetaxel and oxaliplatin may more safety and still efficacy, and the novel additional nutritive support agents may enhance safety about chemotherapy toxicity.

2. Protocol design

2.1 Propose

This is a pilot study for using docetaxel, oxaliplatin, combination chemotherapy, with novel additional nutritive support agents in stage III

non-small cell lung cancer.

Taxanes-based and platinum-based chemotherapy were both standard treatments in several kinds of neoplasm. Combining more than one drug may kill more tumor cells, but also with higher toxicity. We initial this study for demonstrating clinical benefit and safety of docetaxel combined oxaliplatin chemotherapy in non-small cell lung cancer.

The objectives of novel additional nutritive support agents were focus on control adverse effects, and combined with standard medication.

Quality of life, adverse effects, and clinical benefits all would be recorded in this study for make sure drug efficacy and safety.

2.2 Primary Endpoint

- Find out each maximum clinical dose level of docetaxel, and oxaliplatin in combination chemotherapy
- Evaluate patients tumor response rate after received 2 months chemotherapy
- Manager toxicity of this combination regimen in non-small cell lung cancer patients

2.3 Second Endpoint

- Evaluate quality of life during the chemotherapy period

- Follow next treatment option after 6 treatment (2 courses) of chemotherapy
- Follow up overall survival of patients after receiving this regimens

2.4 Regimen

This combination chemotherapy is a 2 monthly schedule, patients would receive docetaxel 30 mg/m^2 and oxaliplatin 45 mg/m^2 weekly for 3 weeks, then one week rest. Patient would total received 6 times weekly chemotherapy treatment, than evaluate by RECEIST guideline.

Dexamethasone and serotonin receptor antagonist were given for standard weekly docetaxel regimen for antiemetic and prophylactic fluid retention.^{21,22} Vitamin B12 and folic supplemented as pemetrexed treatment but modified. Folic acid (350 to $1,000 \mu\text{g}$) orally daily since docetaxel and oxaliplatin chemotherapy treatment day 1 to 14. Vitamin B12 ($1,000 \mu\text{g}$) was given intramuscularly 1 to 2 weeks before the first dose of chemotherapy and was administered $250 \mu\text{g}$ approximately each 2 weeks throughout study.

After received chemotherapy, hematological data, neurotoxicity, and other adverse effects of patients would be monitored until recovery for delay 1 week before received next chemotherapy. The adverse effects during treatment periods would be referenced for adjustment each dose

level of docetaxel and oxaliplatin.

When patient received 6 course of regimen, by RECIST guideline for evaluated tumor response, and base on the disease status, physician could decide withdraw patient for disease progression or received surgery.

Treatment schedule is a 3 weekly treatment, then rest 1 week. The least treatment is 6 courses regimen, then use computer tomography with RECIST guideline for evaluated tumor response. Safety issues and next treat options were all followed items for secondary objective. Withdraw criteria are including 2 times dose-reduced, disease progression, or patient issue.

2.5 Safety Evaluation and Dosage Modification

2.5.1 Safety Evaluation Items

Before patients received combination regimen, patients should be monitored hematological data, performances status, Lung Cancer Symptom Scale (LCSS), and adverse effects according to the National Cancer Institute – Common Toxicity Criteria (NCI-CTC) version 3.

If patient experiences less than grade 1 adverse effects and recovery during 7days period, patient could receive next dose level of docetaxel. After received addiction dose level of docetaxel, if patient could tolerance

and recovery during the period, patient should maintain the same dose docetaxel and next dose level oxaliplatin. If patient with adverse effect between grade 1~2 during previous course, he should maintain the same dose for chemotherapy.

When patient experiences more than grade 3 adverse effects, he should delay next course chemotherapy until recovery, and received reduced one dose level chemotherapy. The reduced chemotherapy dose level of each agent should base on the major toxicity profiles of them.

2.5.2 Dose Adjustments Guideline

Each Dose Level of Chemotherapy (please chose one of them)

Dose Level	Docetaxel (mg/m²)	Oxaliplatin (mg/m²)
-2	20	35
-1	25	40
0	30	45
1	35	50
2	40	55

Docetaxel

Neutropenia and leucopenia evaluation were accorded on NCI-CTC hematological grade. Hematological side effect is major adjustment criteria for dose reducing. When more than grade 3 adverse hematological effects happened, patient should delay next course treatment during 7 days, and reduced 1 dose level for next treatment.

Oxaliplatin

Adverse affects of oxaliplatin are similar to those of cisplatin, but nausea and vomiting, nephrotoxicity, and myelosuppression, seem to be less marked. Raised liver enzyme values may occur. Neurotoxicity can be dose-limiting. Peripheral neuropathy occurs in 85 to 95% of patients given oxaliplatin; pain, functional impairment, and loss of tendon reflexes may develop. Pulmonary fibrosis, potentially fatal, has also been reported. Extravasation of oxaliplatin can cause local pain and inflammation; complications may sometimes be severe, including necrosis.

Neurotoxicity evaluation would be accorded on NCI-CTC and an oxaliplatin-specific scale (grade 0-3, see appendix 5.4).

- I. When patient without any neurotoxicity after received two course oxaliplatin treatment, he could receive up dose level of oxaliplatin.
- II. Only patient with OS scale grade 1 or less than grade 2 NCI-CTC neurotoxicity, patient could maintain the same dose level to treatment.
- III. If there were grade 2 OS scale adverse effect, patient should reduce one dose level oxaliplatin.
- IV. If there was grade 3 OS scale happened, patient should withdraw from this study.

3. Criteria

3.1 Inclusion Criteria

- a. Patient with histological biopsy for non-small cell lung cancer,

- and diagnosis more than stage III
- b. Patient without radiotherapy previously, and never received oxaliplatin or docetaxel before
 - c. Patients were aged 18 to 75 years
 - d. Patient's WHO performance status required ≤ 1 , and life expectancy > 3 months
 - e. Patient with measurable lesion by RECIST criteria
 - f. Subjects must have absolute neutrophil count (ANC) ≥ 1500 /mm³, platelet count $\geq 100,000$ /mm³, and hemoglobin ≥ 10.0 g/dL
 - g. Subjects must have normal renal function
 - h. Subjects must have adequate hepatic function (normal bilirubin, and AST and ALT ≤ 3 x upper limit of normal)
 - i. Subjects are willing to comply with the study protocol and sign the informed consent form

3.2 Exclusion Criteria

- a. Subjects who are pregnant, lactating or of childbearing potential not using effective contraceptives
- b. Subjects who have active or uncontrolled infection, cardiovascular disease (cardiac failure, myocardial infarction within the previous 6 months, uncontrolled hypertension or arrhythmia)
- c. Subjects who have other major illness that, in the investigator's judgment, will substantially increase the risk associated with the

subject's participation in this study

- d. Subjects who are known of hypersensitivity to taxanes or platinum agents
- e. Subjects have received major surgery, radiotherapy, or chemotherapy within 28 days prior to study entry (42 days if prior chemotherapy included mitomycin C or a nitrosourea)
- f. Subjects have finished another clinical trial more than 30 days

4. Statically Section

We initial a MiniMax Design minimizes the maximum sample size in this pilot study. Based on the author Ohe, Y. weekly docetaxel and cisplatin in non-small cell lung cancer study, the non-elderly patient showed a 27 % response rate, and elderly patient showed 58 %.²³ This is the most like regiment to our study. So we hypothesis the response rate of bad and good are 27 %, and 58 %. Calculated statically of MiniMax Design in minimizes to the maximum total sample sizes were between 22 to 25, and two stage method for enrolled patients.

For a total of 25 subjects, 8 will be accrued during stage 1 and 17 during stage 2.

Given that the 'true' response probability is 27%, there is a 62.82% probability of ending the trail during stage 1. However, if the 'true' response probability is 58% then there is a 6.34% probability that the trail will be stopped in stage 1.

The alpha level of the design is 0.04 and the power is 0.9.

If 2 or fewer responses are observed during the first stage then the trail is stopped early. If 10 or fewer responses are observed by the end of the trail then no further investigation of the drug is warranted.

Final report would analysis about tumor response, adverse effects, quality of life, time to treatment failure, and next option after received 6 courses of chemotherapy, etc. And all patients would also follow survival benefit by 3 months contact.

5. Medication References

5.1 Docetaxel (Taxotere)

Docetaxel is a semisynthetic taxane similar to paclitaxel. It is manufactured from a taxane precursor derived from the needles of the European yew tree *Taxus baccata*. Docetaxel is used for locally advanced or metastatic breast cancer. It may be used as first-line treatment with doxorubicin; in the treatment of refractory disease, it is used alone or with capecitabine. In the treatment of breast cancer patients with metastatic disease who overexpress HER2 (human epidermal growth receptor 2), docetaxel may be used with trastuzumab as initial therapy. For adjuvant treatment of operable, node-positive breast cancer, docetaxel is given with doxorubicin and cyclophosphamide.

Docetaxel is also indicated for the treatment of locally advanced or metastatic non-small cell lung cancer, either with cisplatin for initial treatment of unresectable disease, or after failure of previous platinum-based chemotherapy. It may be used in hormone-refractory metastatic prostate cancer, and is being investigated in various other malignant neoplasms including the palliative treatment of cancers of the head and neck.

Docetaxel is given by intravenous infusion in glucose 5% or sodium chloride 0.9% at a concentration not exceeding 0.74 mg/mL. Infusion is normally over 1 hour. The licensed dose for docetaxel as a single agent in the treatment of breast cancer after failure of previous chemotherapy is 60 to 100 mg/m² once every 3 weeks. A dose of 75 mg/m² is given in combination therapy with doxorubicin, or capecitabine, or when used as adjuvant therapy with doxorubicin and cyclophosphamide. The dose for non-small cell lung cancer is 75 mg/m² once every 3 weeks, for both first-line combination therapy and monotherapy after failure of previous chemotherapy. Premedication with an oral corticosteroid, such as dexamethasone 16 mg daily, for 3 days starting 1 day before docetaxel is recommended.

For prostate cancer, the dose of docetaxel is 75 mg/m² once every 3 weeks, with prednisone 5 mg orally twice daily given continuously. The use of prednisone reduces the need for a premedication corticosteroid; dexamethasone 8 mg may be given at 12 hours, 3 hours, and 1 hour before docetaxel.

Regular blood counts are required, and dosage in subsequent courses should be reduced in patients who experience severe or febrile neutropenia, or severe cutaneous reactions or peripheral neuropathy. The dose of docetaxel should be reduced in hepatic impairment.

On intravenous dosage docetaxel is rapidly distributed to body tissues. Docetaxel is more than 95% bound to plasma proteins. It is extensively metabolised via hepatic cytochrome P450 isoenzyme CYP3A and excreted chiefly in the faeces as metabolites. Only about 6% of a dose is excreted in urine. The terminal elimination half-life is about 11 hours. Clearance is reduced in hepatic impairment.

5.2 Oxaliplatin (Eloxatin)

Oxaliplatin is a platinum-containing complex similar to cisplatin. It is given with fluorouracil and folinic acid in the treatment of metastatic colorectal cancer and in the adjuvant treatment of stage III (Dukes C) colon cancer. The recommended dose is 85 mg/m² by intravenous infusion over 2 to 6 hours, dissolved in 250 to 500 mL of glucose 5%. The dose may be repeated at intervals of 2 weeks if toxicity permits, reduced according to tolerance. In the adjuvant setting, oxaliplatin is given for 12 cycles. Following persistent neurotoxicity or recovery from severe adverse effects the manufacturers recommend an initial reduction to 65 mg/m² in metastatic colorectal cancer, and to 75 mg/m² when given as adjuvant treatment. Oxaliplatin should always be

administered before fluoropyrimidines.

After intravenous doses, oxaliplatin is widely distributed throughout the body. It binds irreversibly to red blood cells, which can prolong the half-life of the drug. The mean terminal half-life has been variously stated to be 273 hours and 391 hours. Oxaliplatin is extensively metabolized to both inactive and active compounds and is predominantly excreted in the urine.

5.3 Dexamethasone

Dexamethasone is a class drug of aminoglycoside/corticosteroid, and be approved by FDA for several indication. For chemotherapy, dexamethasone could use for prevention several chemotherapy drug induced adverse effects.

FDA labeled indications of dexamethasone are allergic disorders, acute self-limited or acute exacerbations of chronic, cerebral edema, conditions treated by immunosuppression, inflammatory conditions, ophthalmic conditions, including corneal injury, inflammatory conditions, and infective conjunctivitis, and otitis externa.

Non-FDA labeled indications of dexamethasone including antenatal administration in women at risk of preterm delivery, antiemetic , croup.

Dosage of usual dexamethasone

Antiemetic: 20 mg IV before chemotherapy, 8 mg IV/ORAL twice a day for 3 days after chemotherapy

Allergic disorders, acute: first day, dexamethasone sodium phosphate 4-8 mg IM; second and third days, 4 tablets (0.75 mg each) in 2 divided doses each day; fourth day, 2 tablets in 2 divided doses; fifth and sixth days, 1 tablet each day; seventh day, no treatment

Cerebral edema: (dexamethasone sodium phosphate), initial, 10 mg IV, followed by 4 mg IM every 6 hr until symptoms of cerebral edema subside

6. Appendix

6.1 ECOG Performance Status Scale

Score	Description
0	Normal activity
1	Symptoms, but nearly fully ambulatory
2	Some bed time, but needs to be in bed less than 50% of normal daytime
3	Needs to be in bed more than 50% of normal daytime
4	Unable to get out of bed

6.2 Body Surface Area

The Mosteller formula

$$BSA (m^2) = ([Height(cm) \times Weight(kg)] / 3600)^{1/2} \quad \text{e.g. } BSA = \text{SQRT}((cm*kg)/3600)$$

in inches and pounds: $BSA (m^2) = ([Height(in) \times Weight(lbs)] / 3131)^{1/2}$

Weight(Kg)	High(m)															
	1.15	1.2	1.25	1.3	1.35	1.4	1.45	1.5	1.55	1.6	1.65	1.7	1.75	1.8	1.85	1.9
30	0.979	1.000	1.021	1.041	1.061	1.080	1.099	1.118	1.137	1.155	1.173	1.190	1.208	1.225	1.242	1.190
35	1.057	1.080	0.110	1.124	1.146	1.167	1.187	1.208	1.228	1.247	1.267	1.286	1.304	1.323	1.341	1.286
40	1.130	1.155	0.118	1.202	1.225	1.247	1.269	1.291	1.312	1.333	1.354	1.374	1.394	1.414	1.434	1.374
45	1.199	1.225	0.125	1.275	1.299	1.323	1.346	1.369	1.392	1.414	1.436	1.458	1.479	1.500	1.521	1.458
50	1.264	1.291	0.132	1.344	1.369	1.394	1.419	1.443	1.467	1.491	1.514	1.537	1.559	1.581	1.603	1.537
55	1.325	1.354	0.138	1.409	1.436	1.462	1.488	1.514	1.539	1.563	1.588	1.612	1.635	1.658	1.681	1.612
60	1.384	1.414	0.144	1.472	1.500	1.528	1.555	1.581	1.607	1.633	1.658	1.683	1.708	1.732	1.756	1.683
65	1.441	1.472	0.150	1.532	1.561	1.590	1.618	1.646	1.673	1.700	1.726	1.752	1.778	1.803	1.828	1.752
70	1.495	1.528	0.156	1.590	1.620	1.650	1.679	1.708	1.736	1.764	1.791	1.818	1.845	1.871	1.897	1.818
75	1.548	1.581	0.161	1.646	1.677	1.708	1.738	1.768	1.797	1.826	1.854	1.882	1.909	1.936	1.963	1.882
80	1.599	1.633	0.167	1.700	1.732	1.764	1.795	1.826	1.856	1.886	1.915	1.944	1.972	2.000	2.028	1.944
85	1.648	1.683	0.172	1.752	1.785	1.818	1.850	1.882	1.913	1.944	1.974	2.003	2.033	2.062	2.090	2.003
90	1.696	1.732	0.177	1.803	1.837	1.871	1.904	1.936	1.969	2.000	2.031	2.062	2.092	2.121	2.151	2.062
95	1.742	1.780	0.182	1.852	1.887	1.922	1.956	1.990	2.022	2.055	2.087	2.118	2.149	2.179	2.210	2.118
100	1.787	1.826	0.186	1.900	1.936	1.972	2.007	2.041	2.075	2.108	2.141	2.173	2.205	2.236	2.267	2.173
105	1.831	1.871	0.191	1.947	1.984	2.021	2.056	2.092	2.126	2.160	2.194	2.227	2.259	2.291	2.323	2.227
110	1.875	1.915	0.195	1.993	2.031	2.068	2.105	2.141	2.176	2.211	2.245	2.279	2.312	2.345	2.378	2.279
115	1.917	1.958	0.200	2.038	2.077	2.115	2.152	2.189	2.225	2.261	2.296	2.330	2.364	2.398	2.431	2.330
120	1.958	2.000	0.204	2.082	2.121	2.160	2.198	2.236	2.273	2.309	2.345	2.380	2.415	2.449	2.483	2.380

6.3 Tumor Response Evaluation Method :

- Response Evaluation Criteria in Solid Tumors (RECIST)²⁴

6.4 Toxicity According References

- Common Terminology Criteria for Adverse Events v3.0 (CTCAE)
- Oxaliplatin-specific scale : All of defined as follows-grade 1, hypothesia or paresthesia which completely resolved before the next cycle; grade 2, hypothesia or paresthesia which between cycles, without functional impairment; grade 3, permanent functional impairment.

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Protocol Signature Page

Study Titles

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Agreements

The Investigator agree to follow to the protocol as outlined and this study will be conducted in accordance with International Conference on Harmonization (ICH) guidelines, Good Clinical Practice (GCP) standards, the Declaration of Helsinki, and local ethical and legal requirements.

Principal Investigator

Dr.

Date

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