

Gemcitabine in advanced non-small cell lung cancer: A phase II study

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RESUMEN

Gemcitabina es un agente activo en el tratamiento del cáncer de pulmón (CPCNP). El tratamiento semanal con gemcitabina, como agente único, ha mostrado respuestas del 20 al 26%. Este estudio fase 2 fue realizado para determinar la eficacia y seguridad de gemcitabina 1000 mg/m², administrado semanalmente. Por tres semanas, seguido de una de descanso (ciclos de 28 días): los pacientes requirieron tener evidencia histológica de CPCNP y enfermedad avanzada; estado de desempeño de Zubrod de 0 a 2 y enfermedad medible. No se permitió que hubieran recibido tratamiento previo. Veinte pacientes, diez hombres y diez mujeres con una edad promedio de 60 años fueron incluidos en el estudio. La mayor parte de los pacientes (doce pacientes, 60%) tuvieron EC IIb y, diagnóstico de adenocarcinoma (trece pacientes, 65%). Cuatro pacientes (20%) tuvieron EC IIIa y otros cuatro (20%) tuvieron EC IV, siete pacientes (35%) tuvieron variedad histológica epidermoide. Los pacientes recibieron un total de 62 ciclos y un promedio de 3.1 ciclos de terapia con gemcitabina. De los dieciocho pacientes que se incluyeron para evaluar eficacia, en seis se obtuvo respuesta parcial con un porcentaje de respuesta del 33.3%.

La supervivencia media fue de siete meses (dos a 15 meses) con un tiempo medio libre de enfermedad de 3.5 m (1-15 meses) y un año de supervivencia del 22.2%. Toxicidad hematológica grado 3 y 4 de la Organización Mundial de la Salud (OMS) fue observada en menos del 2% de todos los ciclos. La toxicidad más común grado 3 y 4 nohematológica fue náusea y vómito observada en menos del 5% de los ciclos.

Elevación transitoria de transaminasas se observó en menos del 4% de los ciclos. Un paciente presentó hepatitis fulminante y rash generalizado que, a consideración de los investigadores, se debió a una reacción de hipersensibilidad por toxicidad de la gemcitabina. En conclusión, gemcitabina como agente único en administración semanal de 1000 mg/m² es segura y efectiva en el tratamiento del CPCNP avanzado.

Palabras clave: Gemcitabina, cáncer de pulmón, células no pequeñas.

ABSTRACT

Gemcitabine is an active agent for treatment of advanced non-small cell lung cancer (NSCLC). Weekly treatment with single-agent gemcitabine has shown response rates of 20% to 26%. This Phase II trial was conducted to determine the efficacy and safety of 1000 mg/m² gemcitabine administered weekly for 3 weeks followed by 1 week or rest (28-day cycle). Patients were required to have histologic evidence of NSCLC and advanced disease, a Zubrod's performance status of 0 to 2, and measurable disease. No prior therapy was permitted. Twenty patients, 10 men and 10 women, having a mean age of 60 years enrolled in the study. Most patients (12 patients, 60%) had Stage IIIB disease and adenocarcinoma (13 patients, 65%). Four (20%) patients each had Stage IIIA and Stage IV disease and 7 (35%) patients had squamous cell tumors. Patients received a total of 62 cycles and an average of 3.1 cycles of gemcitabine therapy. Of the 18 patients included in the efficacy analyses, six were partial responders with a total response rate of 33.3%.

Mean survival time was 7 months (2 to 15 months), mean progression-free survival time was 3.5 months (1 to 15 months), and the 1-year survival rate was 22.2%. World Health Organization (WHO) Grade 3 or 4 hematologic toxicities were observed in less than 2% of all cycles. The most common Grade 3 or 4 nonhematologic toxicities were nausea and vomiting observed in < 5% of cycles.

Transient transaminase elevations were observed in < 4% of cycles. One patient presented with fulminant hepatitis and generalized vesicular rash believed by the investigators to be a hypersensitivity reaction due to gemcitabine toxicity. In conclusion, single-agent gemcitabine administered as a weekly dose of 1000 mg/m² is safe and effective in the treatment of patients with advanced NSCLC.

Key words: Gemcitabine, lung cancer, non-small cell.

INTRODUCTION

Lung cancer, a worldwide health problem, is the main cause of death by cancer in Mexico. In 1995, 1631 new cases of lung cancer were diagnosed. Most of these cases involved non-small cell lung cancer (NSCLC) and are expected to increase due to smoking.¹ At the time of diagnosis, 70% of patients with NSCLC have locally advanced Stage IIIa, IIIb, or IV disease, in which

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palliative therapy is often employed since surgery is generally only useful in localized disease. Thus, the overall survival and prognosis is poor attesting to an 87% death rate for these patients.²

The lack of success of various chemotherapy regimens against NSCLC necessitates continued testing of new agents. In recent years, a number of promising new drugs have been identified with different mechanisms of action and encouraging toxicity profiles that exert effective activity in advanced NSCLC with response rates ranging from 14% to 33%.³ One of these, gemcitabine hydrochloride, a novel pyrimidine nucleoside, is analogous to the antimetabolite cytosine arabinoside (ara-C), but possesses unique pharmacokinetic and antitumor properties that produce cytotoxic activity in range of human neoplasms. These properties include a greater membrane permeability, a greater affinity for deoxycytidine kinase, and longer intracellular retention with a prolonged inhibition of DNA synthesis.⁴

Single-agent gemcitabine treatment in patients with advanced NSCLC not treated previously with chemotherapy, resulted in objective response rates of 20% to 26%.⁵ In addition, in Phase I and II trials in which doses varied from 800 to 1250 mg/m² per week, gemcitabine was found to have acceptable toxicity. The efficacy results in these trials, however, suggested that the 800-mg/m² dose was not optimally effective. Those patients who received a dose below 900 mg/m² had a 14.3% response rate compared to 21.4% for those patients who received doses above of 900 mg/m².^{6,7} These results support the continued testing of gemcitabine at doses above 800 mg/m² in an attempt to improve therapeutic benefit without increasing toxicity. In this Phase II study, the effectiveness and toxicity of 1000 mg/m² gemcitabine administered weekly were assessed in patients with advanced NSCLC not treated previously with chemotherapy.

PATIENTS AND METHODS

This was a 1-year, Phase II study of gemcitabine in patients with advanced NSCLC conducted from April 1996 to May 1997. Inclusion criteria included: histologic diagnosis of State III or IV NSCLC not amenable to curative surgery or radiotherapy; no previous chemotherapy; activity level of 0 to 2 on the Zubrod performance scale; (clinically measurable disease defined as bidimensionally measurable lesions with clearly defined margins as assessed by physical examination or image studies;) life expectancy of more than 2 months, and adequate bone marrow reserves defined by a white blood cell count $> 3.5 \times 10^9/L$, a platelet count $>$

$100 \times 10^9/L$, and a hemoglobin count > 10 g/L. Exclusion criteria for included: presence of active infection, central nervous system metastasis; inadequate liver function (bilirubin > 1.5 mg/dL *vs versus*, abnormal prothrombin time or partial thromboplastin time > 1.5 times control, alanine transaminase (ALT) or aspartate transaminase (AST) > 3 times normal or > 5 times normal in patients with known metastatic disease in the liver); calcium levels above the upper limit of normal; pregnancy or lactation; serious concomitant medical conditions incompatible with the study; second primary malignancy except for *in situ* carcinoma of the cervix or adequately treated basal cell carcinoma of the skin.

Treatment consisted of 1000 mg/m² gemcitabine administered intravenously over 30 minutes on Day 1, 8, and 15 followed by 1 week of rest; this constituted a 28-day cycle.

Hematologic toxicity was assessed using the World Health Organization (WHO) grading scale, before each infusion each infusion. Doses were adjusted (reduced, omitted) or delayed depending on the severity of hematologic and nonhematologic toxicities. Patients received up to a maximum of 8 cycles after achieving best response.

Antiemetics were permitted during treatment as needed

Tumor response was assessed after each cycle, using imagine studies comparing baseline *vs* posttreatment images. In order to describe disease status and the type of response to treatment, WHO criteria was used as follows: Complete response was defined as the disappearance of all known disease as determined by two separate observations not less than 4 weeks apart. Partial response was defined as a decrease of at least a 50% in total tumor size with two observations not less than 4 weeks interval, and no appearance of new or progressed lesions. Stable disease was indicated if a 50% decrease in total tumor size or a 25% increase in the size of measurable lesions could not be demonstrated.

Progressive disease was defined as a minimum increase of 25% in the size of at least one measurable lesion or the appearance of new lesions.

Patients were included in the efficacy analyses if they received at least three gemcitabine doses. The safety analyses included patients who received at least one dose of gemcitabine. Total response rate, mean progression-free survival time, mean survival time, and the survival rate at 1 year were computed. The duration of survival time was defined as the time from the initial dose to the time of death.⁹ Safe-

ty was evaluated using WHO toxicity criteria for laboratory and nonlaboratory parameters.

RESULTS

Twenty patients with equal numbers of males and females and a medium age of 60 years were enrolled in this study. Most patients had Stage IIIB disease (12 patients, 60%) and adenocarcinoma (13 patients, 65%). Patient characteristics are presented in *table I*.

Patients received a total of 62 cycles (range 1 to 8 cycles) and an average of 3.1 cycles of gemcitabine therapy.

Two patients were not included in the efficacy analyses because they did not receive at least three doses of gemcitabine. Of the 18 patients included in the efficacy analyses, there were no complete responders; however, six patients were partial responders resulting in a total response rate of 33.3%. Eight (44.5%) patients achieved stable disease. Mean survival time was 7 months (range 2 to 15 months), mean progression-free survival time was 3.5 months, and the 1-year survival rate was 22.2% (*Figure 1*).

Hematologic and nonhematologic toxicities and their associated grades are shown in *tables II and III*. Hematologic toxicities were generally mild; severe

(Grade 3 or 4) toxicities were observed in < 2% of all therapy cycles. The most frequent reported Grade 3 or 4 hematologic toxicities were anemia and neutropenia. There were not severe toxicity ratings reported for thrombocytopenia. The most common Grade 3 or 4 nonhematologic toxicities were nausea and vomiting observed in 4.8% of cycles.

Transient transaminase elevations were observed in 3.8% of all cycles, although the increases were generally mild and did not require dose modifications for most patients.

One patient, however, experienced fulminating hepatitis and generalized vesicular rash with various lesions (erythema spots, vesicles) that began suddenly on the third week of gemcitabine administration. Because the event appeared suddenly and the patient was negative for the hepatitis virus, the investigators considered the hepatitis was a toxic effect of gemcitabine and therefore likely related to therapy. In addition, histologic results of a liver biopsy supported a drug toxicity etiology.

DISCUSSION

The management of NSCLC is evolving due to availability of new drugs. The results of this study support

Table I. Patient characteristics.

Total	20
Male	10 (50%)
Female	10 (50%)
Age, years	
Median	60
Range	29-74
Stage	
III A	4 (20%)
III B	12 (60%)
IV	4 (20%)
Histology	
Squamous	7 (35%)
Adenocarcinoma	13 (65%)

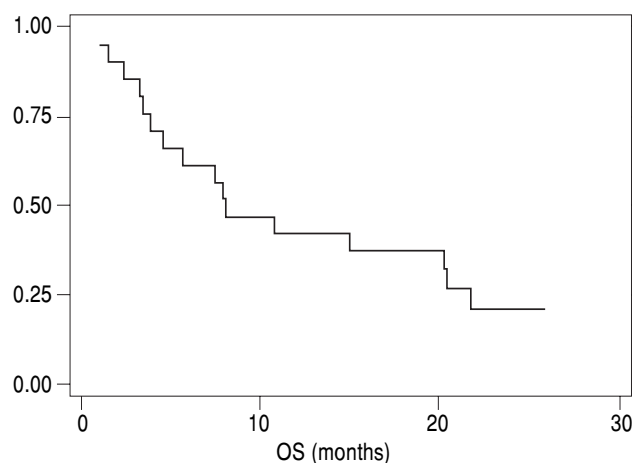


Figure 1. Kaplan-Meier overall survival estimate

Table II. Hematological toxicity.

WHO grade	0		1		2		3		4	
	No.	%	No.	%	No.	%	No.	%	No.	%
Leucocytes	45	72.5	14	22.5	2	3.2	1	1.6	0	0
Granulocytes	51	82.2	7	11.2	3	4.8	1	1.6	0	0
Hemoglobin	42	67.7	17	27.4	2	3.2	1	1.6	0	0
Platelets	62	100	0	0	0	0	0	0	0	0

Table III. Non-hematological toxicity.

WHO grade	0		1		2		3		4	
	No.	%	No.	%	No.	%	No.	%	No.	%
Alkaline phosphatase	39	62.9	23	37.1	0	0	0	0	0	0
Transaminases*	49	94.2	2	3.8	0	0	0	0	1	2
Nausea/vomiting	39	62.9	14	22.6	6	9.7	2	3.2	1	1.6
Diarrhea	54	87.1	4	6.5	4	6.5	0	0	0	0
Fever	55	88.7	6	9.7	1	1.6	0	0	0	0
Cutaneous	52	83.9	6	9.7	3	4.8	1	1.6	0	0
Hair	58	93.5	1	1.6	1	1.6	2	3.2	0	0
Constipation	57	91.9	4	6.5	1	1.6	0	0	0	0
Hematuria	57	91.9	5	8.1	0	0	0	0	0	0
Myalgias	61	98.4	1	1.6	0	0	0	0	0	0
Consciousness	60	96.8	0	0	2	3.2	0	0	0	0
Peripheral neurotoxicity	61	98.4	1	1.6	0	0	0	0	0	0
Pulmonary	60	96.8	2	3.2	0	0	0	0	0	0

* Not evaluated in 10 cycles.

the use of gemcitabine as a safe and effective treatment of patients with advanced NSCLC. The 33.3% response rate observed with gemcitabine in this study compares favorably with the 20% rates observed with other effective drugs used as single agents against NSCLC,⁹ and is superior to the 14.3% rate observed in studies that used lower gemcitabine doses (< 900 mg/m²/week).⁶⁻⁸

In this study, the effectiveness of the 1000-mg/m² dose was not accompanied by increased toxicity. The toxicity profile of gemcitabine was mild and the drug was well tolerated. Severe (Grade 3 or 4) hematologic toxicities occurred in < 2% of administered cycles and no patients required hospitalization or intervention for neutropenic fever. As for nonhematologic toxicities, the most severe were nausea and vomiting present in < 5% of cycles. The prophylactic use of a 5-HT₃ receptor antagonist for nausea was not required routinely and when emesis did occur, it was easily controlled. One patient presented hepatic toxicity, which has been reported infrequently (< 1%) in other Phase I and II gemcitabine trial.¹⁰ It was not necessary to suspend treatment or adjust the dose of gemcitabine in any patients.

In conclusion, single-agent gemcitabine is an effective and well tolerated first-line treatment in patients with NSCLC and because of its mild toxicity profile, it can be used alone or in combination with other agents.

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