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Phase I/II trial of pemetrexed plus nab-paclitaxel in advanced solid tumor patients with emphasis on non-small cell lung cancer

Cheryl Ho,

British Columbia Cancer Agency, 600 W 10th Avenue, Vancouver, BC V5Z 4E6, Canada

Angela M. Davies,

Novocure, New York, NY, USA

Randeep S. Sangha,

Cross Cancer Institute, Edmonton, AB, Canada

Derick Lau,

University of California Davis Medical Center, Sacramento, CA, USA

Primo Lara Jr.,

University of California Davis Medical Center, Sacramento, CA, USA

Helen K. Chew,

University of California Davis Medical Center, Sacramento, CA, USA

Laurel Beckett,

University of California Davis Medical Center, Sacramento, CA, USA

Philip C. Mack,

University of California Davis Medical Center, Sacramento, CA, USA

Jonathan W. Riess, and

University of California Davis Medical Center, Sacramento, CA, USA

David R. Gandara

University of California Davis Medical Center, Sacramento, CA, USA

Summary

Background—Despite advances in targeted therapies, there is an ongoing need to develop new and effective cytotoxic drug combinations in non-small cell lung cancer (NSCLC). Based on preclinical demonstration of additive cytotoxicity, we evaluated the safety and efficacy of combining pemetrexed and nanoparticle albumin bound (nab) paclitaxel with a focus on NSCLC for phase II expansion.

Methods—A 3+3 dose-escalation design was used to determine the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D). Three dose levels were tested: pemetrexed

C. Ho cho@bccancer.bc.ca.

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500 mg/m² day 1 and nab-paclitaxel day 1 at 180, 220, & 260 mg/m² every 21 days. Phase II eligibility included advanced NSCLC, 2 line prior therapy, PS 0–1, adequate organ function. Primary endpoint for further study was response rate (RR) 25 %.

Results—Planned dose escalation was completed without reaching the MTD. The RP2D was pemetrexed 500 mg/m² and nab-paclitaxel 260 mg/m². The phase II portion accrued 37 pts before early closure due to increasing first-line pemetrexed/platinum doublet use in non-squamous NSCLC. In 31 assessable phase II patients there were 5 partial responses, 12 stable disease, 14 progressive disease. The median overall survival was 8.8 months; progressive disease 4.4 months and disease control 15.6 months.

Conclusions—Pemetrexed 500 mg/m² day 1 with nab-paclitaxel 260 mg/m² was feasible and well tolerated. The phase II component demonstrated activity in second/third-line therapy of advanced NSCLC; response rate 14 % and disease control rate 46 %. Treatment practice patterns of advanced NSCLC have evolved; further trials of this regimen are not planned.

Keywords

Phase II; Pemetrexed; Nab-paclitaxel; Nanoparticle albumin bound paclitaxel; Non small cell lung cancer

Introduction

In 2013 an estimated 228,190 new cases of lung cancer will be diagnosed and 159,480 lung cancer deaths will occur in the United States [1]. Lung cancer results in more deaths than colorectal, breast and prostate cancer combined annually. Advances in the treatment of non-small lung cancer (NSCLC) in the past decade include: third generation platinum doublets, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in EGFR mutation positive disease, maintenance systemic therapy and second/third line treatments that improve survival [2–8]. In spite of these improvements the median survival for patients remain limited and new therapeutic options need to be explored.

Pemetrexed exerts its cytotoxic effects through inhibition of the folate pathway; it is a multitargeted antifolate that inhibits several important enzymes in cell proliferation including thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyl transferase [9]. After cellular uptake, its polyglutamated form results in prolonged intracellular retention and enhanced cytotoxicity.

Pemetrexed has been part of the standard of care for NSCLC patients since 2004 and specifically non-squamous disease since 2007. A Phase III non-inferiority trial for survival demonstrated that in second line NSCLC, pemetrexed or docetaxel had comparable efficacy [8]. Based on this study pemetrexed received FDA approval for second line treatment of advanced NSCLC. In 2008 it received its indication for first line platinum-based therapy in locally advanced or metastatic NSCLC and 2009 as maintenance therapy for patients whose disease has not progressed after four cycles of platinum-based first-line palliative intent chemotherapy [2, 4].

Nanoparticle albumin-bound (nab)-paclitaxel is a biologically interactive nanoparticle, combining albumin with paclitaxel [10]. This composition provides a novel approach of increasing intra-tumoral concentration of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell wall, thereby breaching the blood/tumor interface. Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. Nab-paclitaxel has a better toxicity profile with respect to neutropenia and neuropathy compared to solvent-based (sb) paclitaxel.

Nab-paclitaxel was approved in NSCLC based on a phase III trial comparing nab-paclitaxel/carboplatin with sbpaclitaxel/carboplatin in first line stage IIIB/IV disease [11] which showed a higher response rate (RR) with nab-paclitaxel and similar progression free survival (PFS); overall survival (OS) was 12.1 versus 11.2 months compared to sb-paclitaxel. Safety analysis noted a significant reduction in peripheral neuropathy, patient-reported neuropathy and hearing loss.

Preclinical work with pemetrexed and paclitaxel has suggested an additive effect of the combination. In H460 human lung adenocarcinoma xenografts in nude mice, the combination resulted in increased tumor growth delay compared to either drug alone [12]. Teicher et al. also noted that paclitaxel and pemetrexed demonstrated additive effects in both MX-1 breast cancer and H460 NSCLC xenografts [13]. Schedule dependent investigations of these agents were conducted in several different cell lines [14]. In A549 lung cancer cells, antagonism was observed when both drugs were delivered simultaneously; however synergy was noted when exposure to pemetrexed preceded paclitaxel.

Nab-paclitaxel, and pemetrexed have independent mechanisms of cytotoxicity; pemetrexed exerts its anti-cancer activity by disrupting folate dependent metabolic processes whereas nab-paclitaxel targets microtubules involved in mitosis. Preclinical investigations suggest that these different antitumor approaches can be combined to augment efficacy. These agents have overlapping hematologic toxicity. However, studies have indicated less neutropenia with nab versus sb paclitaxel. Here we report a phase I/II trial evaluating the safety, tolerability and efficacy of combination pemetrexed with nab-paclitaxel in patients with advanced solid tumors with emphasis on NSCLC.

Patients and methods

Patient selection

For the phase I component, patients with cytologically or histologically proven advanced solid tumors, any number of prior chemotherapy regimens and performance status (PS) 0–2 were eligible. For the phase II component, patients with cytologically or histologically proven stage IIIB (pleural effusion)/IV NSCLC by AJCC 6th Ed. and patients that progressed or recurred after first-line therapy were eligible. Patients must have received platinum-based therapy and no more than 2 previous chemotherapy regimens for advanced NSCLC (for patients with recurrent stage III disease up to 2 prior treatments including prior adjuvant or concurrent chemoradiotherapy were allowed), have measurable disease by RECIST 1.0¹⁶ and PS 0–1.

Other eligibility criteria included: age ≥ 18 years, life expectancy ≥ 12 weeks, adequate renal function (creatinine clearance of ≥ 45 ml/min), adequate liver function (AST and ALT ≤ 2.5 X upper limit of normal (ULN) and bilirubin ≤ ULN), adequate bone marrow function (platelets ≥ 100,000 cells/mm³ and ANC ≥ 1,500 cells/mm³). Prior chemotherapy must have been completed ≥ 4 weeks and radiation must have been completed ≥ 2 weeks prior to start of therapy and all significant treatment related toxicities had to be resolved. Patients with asymptomatic treated brain metastasis (surgical resection or radiotherapy) were permitted if they were neurologically stable and off steroids and anticonvulsants for at least 4 weeks.

Exclusion criteria included: pregnancy or breast-feeding, other active malignancy, uncontrolled inter-current illness, presence of third space fluid which cannot be controlled by drainage, pre-existing peripheral neuropathy grade ≥ 2 (NCI CTCAE Version 3.0) [15] or prior treatment with pemetrexed or nab-paclitaxel (prior nab-paclitaxel was allowed). The institutional review board at the University of California Davis approved this study. All patients gave written informed consent to participate.

Dose limiting toxicity (DLT) and maximum tolerated dose (MTD) definitions

Dose limiting toxicity (DLT) was defined as any of the following occurring during the first cycle: Grade 4 thrombocytopenia (platelet count < 25,000/mm³), or grade 3 thrombocytopenia (platelet count 25,000 - 49,999/mm³) associated with bleeding, requirement for transfusion, febrile neutropenia, neutropenia (ANC < 1.0 × 10⁹) with documented infection. Non-hematologic DLT included any other grade 3 non-hematologic toxicity that was clinically significant and considered by the investigator to be related to study drug. Alopecia and grade 3 allergic reaction/hypersensitivity with infusion were not considered DLTs.

The maximum tolerated dose (MTD) was defined as the highest dose level at which no more than one patient experienced a DLT, when at least six patients were treated at that dose and were evaluable for toxicity.

Study design and treatment

The dose escalation scheme is summarized in Table 1. Folic Acid (350–1,000 µg) was given 5–7 days prior to first dose of pemetrexed. Vitamin B₁₂ (1,000 µg) was given via intramuscular injection 1 to 2 weeks prior to first dose of pemetrexed and repeated every 9 weeks. Dexamethasone (4 mg) was given twice daily the day before, the day of, and the day after each dose of pemetrexed. Pemetrexed was administered intravenously over 10 min on Day 1 of a 21 day treatment cycle. Nab-paclitaxel was administered intravenously over 30 min following pemetrexed on Day 1 of each cycle. Patients with stable disease or response were allowed to continue on therapy until the time of progression to a maximum of 6 cycles. Treatment was discontinued for disease progression, patient or physicians' request, unacceptable toxicity or treatment delay for more than 3 weeks due to toxicity or inter-current illness.

In the phase I component, a standard 3+3 dose escalation design was used. All treated patients were observed for a minimum of 21 days after the start of the first cycle before accrual to the next dose level was allowed. No intra-patient dose escalation was allowed.

Complete blood counts were obtained weekly and serum chemistries including creatinine and liver function tests were done every cycle. Inter-current toxicities were assessed every 3 weeks.

For hematologic toxicity, pemetrexed and nab-paclitaxel were held for up to 3 weeks if the ANC was $<1.5 \times 10^9$ or platelets $< 100,000/\text{mm}^3$ until count recovery. For non-hematologic toxicity grade 3 pemetrexed and nabpaclitaxel were reduced by one dose level. Dose levels for pemetrexed were 500, 400 and 300 mg/m² and nab-paclitaxel 260, 220, 180 and 140 mg/m² respectively.

Statistical analysis

Results were summarized by descriptive statistics (frequencies, medians and median survival).

For the Phase II portion of the study a two-stage design was used. It was assumed that a response rate of less than 10 % would be considered to provide no substantial improvement over existing therapy. It was assumed that a response rate of 25 % would be considered promising for further study of this combination of drugs. The probability of falsely declaring pemetrexed and nab-paclitaxel as warranting further study is set not to exceed 0.05 (alpha), using a one-sided test. The probability of correctly declaring pemetrexed and nabpaclitaxel warranted further study was set at 0.90 (power). Planned stage 1 accrual was for 31 patients. If four or more responses were observed in the first stage, an additional 24 patients would be accrued during stage 2. If 10 or more responses were observed, we would conclude that the combination was promising and should be considered for further study.

Results

Twelve eligible patients were accrued for the phase I component and 37 patients for the phase II portion. Baseline characteristics are summarized in Table 2. The majority of the phase I patients were male (58 %) with a good performance status (83 %) with a median of 3 prior lines of therapy. The most common tumor type was NSCLC (42 %). In the phase II portion the median age was 63, 62 % male and 68 % current or former smokers. Most patients had a good performance status (81 %). Fifty seven percent had adenocarcinoma, 8 % squamous cell carcinoma and 35 % not otherwise specified. This trial concept was conceived prior to the evidence indicating limited efficacy of pemetrexed in squamous cell carcinoma and therefore this was not an exclusion criterion for enrollment. The phase II portion accrued 37 patients before early closure due to increasing use of first-line pemetrexed/platinum doublet therapy in non-squamous NSCLC.

Dose escalation and toxicities

At dose level 1, 2 and 3 three patients were treated with no dose limiting toxicities. Three additional patients were treated at dose level 3 with no dose limiting toxicities (Table 1). The recommended phase II dose was pemetrexed 500 mg/m² and nab-paclitaxel 260 mg/m² on day 1 of a 21-day cycle.

Toxicity was evaluated based on the standard NCI CTCAE V.3.0 grading criteria [15]. Attributable grade 3 hematologic and non-hematologic toxicities are summarized in Table 3.

Efficacy

The evaluation of response was based on standard RECIST 1.0 criteria [16] (Table 4). Of the 12 patients in the phase I component 10 were assessable for response. Seven patients had stable disease and 3 had progressive disease for a disease control rate of 58 %. Patients received a median of 4 cycles on treatment. The median overall survival was 13.5 months.

In the phase II component in advanced NSCLC, 31 of 37 patients were evaluable for response. There were 5 partial responses, 12 stable disease and 14 with disease progression for a response rate of 14 % and disease control rate of 46 %. Patients received a median of 2 cycles. The median overall survival in the patients with progressive disease was 4.4 months, disease control 15.6 months and entire group 8.8 months.

Discussion

This clinical trial was conducted to determine the safety, feasibility and efficacy of pemetrexed and nab-paclitaxel. Dose escalation through three dose levels was achieved with no dose limiting toxicity and a recommended phase II dose of pemetrexed 500 mg/m² and nab-paclitaxel 260 mg/m² day 1 of a 21 day cycle was established. The toxicity profile indicates that the combination of pemetrexed and nab-paclitaxel is safe and tolerable. The two-staged phase II trial design indicated sufficient response in the first stage to proceed to the second stage. However, changes in clinical practice resulted in slow accrual and a decision was made to terminate the trial early. In the cohort of second and third line NSCLC patients enrolled in the phase II portion, the response rate of 14 %, disease control rate of 46 % and the median survival 8.7 months suggest that the combination was active in this setting.

Other phase II trials have been conducted combining pemetrexed with sb-paclitaxel. Stathopoulos et al. performed a phase I/II study in first line advanced NSCLC. The phase II dose selected was pemetrexed 500 mg/m² and sb-paclitaxel 175 mg/m² [17]. In their study the response rate was 39.6 % with a median survival of 14 months. The combination was well tolerated with no dose limiting toxicities. In the expanded phase II cohort significant toxicities were minimal with 8 % neutropenia, 4 % anemia and 4 % alopecia, similar to our results. This combination could be considered for development as a first line non-platinum based doublet. Prior studies with paclitaxel in NSCLC have suggested that increased dose intensity may improve the median time to tumor progression however; this was associated with increased neurologic toxicity and more severe leukopenia [18]. Our results suggest that higher dose intensity in this combination may be achieved with nab-paclitaxel due to its unique formulation.

A second phase I study was completed combining pemetrexed with sb-paclitaxel using three schedules [19]. The schedule that approximated the one used in our study found a maximum tolerated dose of pemetrexed 400 mg/m² and sb-paclitaxel 135 mg/m² day 1 every 21 days.

The hematologic toxicity rates were high with grade 3 neutropenia observed in 41 % and anemia 8 %. Significant non-hematologic side effects included infection and neuromotor toxicity. This trial was limited by overlapping hematologic toxicities of the two agents and taxane-associated neuropathy. Our study achieved higher doses with acceptable toxicity using nabpaclitaxel.

Since trial inception in 2007, the standard of care in NSCLC has evolved, with more therapeutic strategies for disease management. Two of these advances significantly impacted the accrual to this trial. Scagliotti et al. published a phase III non-inferiority trial comparing cisplatin/pemetrexed versus cisplatin/gemcitabine in chemotherapy naïve advanced NSCLC [2]. The median survival in both arms was 10.3 months. A pre-specified analysis of the impact of NSCLC histology showed that overall survival was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine in patients with adenocarcinoma (12.6 v 10.9 months). The FDA granted approval for this indication in the non-squamous population on September 26, 2008. Subsequently, in 2009, the FDA approved pemetrexed for maintenance treatment of advanced non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy [4]. The phase III trial by Ciuleanu et al. compared maintenance pemetrexed versus placebo and demonstrated an overall survival of 13.4 months versus 10.6 months in the intention to treat group and 15.5 months versus 10.3 months in the non-squamous subgroup. The results of these trials changed patterns of practice in the United States with increased utilization of early (first line and maintenance) pemetrexed in advanced NSCLC.

This phase I/II trial demonstrates that pemetrexed 500 mg/m² and nab-paclitaxel 260 mg/m² day 1 every 21 days is a safe and feasible combination. The phase II component demonstrated activity in second and third line therapy of advanced NSCLC. However, practice patterns with pemetrexed have evolved and further trials of this regimen are not planned.

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Table 1

Dose escalation schema and dose limiting toxicities

Dose level	Pemetrexed+nab-paclitaxel (mg/m2)	Number of patients with DLT/ Number enrolled	DLT
1	500+180	0/3	None
2	500+220	0/3	None
3	500 +260	0/6	None

Table 2

Baseline patient characteristics

	Phase I <i>n</i> =12	Phase II <i>n</i> =37
Median age (years)	70 (51–76)	63 (45–77)
Sex (male/female)	7/5	23/14
Performance status (80/<80)	10/2	30/7
Lines of therapy (median)	3	1
Current/former/never/unknown smoker	1/3/3/5	4/21/7/5
Tumor types		
NSCLC	5	37
Head and neck	2	
Ovarian	2	
Prostate	2	
Breast	1	
NSCLC histology		
Adenocarcinoma	1	21
Squamous cell carcinoma	0	3
Not otherwise specified	4	13

Table 3

Grade 3 hematologic and non-hematologic toxicities observed in all cycles

Grade 3 toxicity	Phase I <i>n</i> =12	Phase II <i>n</i> =37
Anemia	2	2
Leukopenia	1	2
Lymphopenia		2
Neutropenia	2	3
Cardiac ischemia		1
Cellulitis		1
Fatigue	1	
Hypersensitivity		1
Hypoalbuminemia	1	1
Increased transaminases		1
Sensory neuropathy	1	
Vomiting		1

Table 4

Response assessment

	Phase I <i>n</i> =12	Phase II <i>n</i> =37
Median number of cycles	4 (1–6)	2 (1–12) ^a
Complete response	0	0
Partial response	0	5
Stable disease	7	12
Disease control	7 (58 %)	17 (46 %)
Disease progression	3	14
Not evaluable	2	6

^aFour patients were treated for > 6 cycles due to ongoing clinical benefit