A Phase II Study of Irinotecan and Carboplatin in Advanced Non-small Cell Lung Cancer with Pharmacogenomic Analysis: Final Report

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Purpose: We conducted a phase II study of carboplatin and irinotecan in patients with advanced non-small cell lung cancer (NSCLC). In addition, we studied the correlation between certain genotypes of enzymes involved in irinotecan metabolism with efficacy and toxicity.

Patients and Methods: Patients with stage IIIB, IV, or recurrent NSCLC received a combination of irinotecan and carboplatin every 3 weeks at a dose of 200 mg/m2 and area under the curve of 5. Pharmacogenomic analysis was performed on several genes of interest (ABCB1, CYP3A4*1B, ERCC2, GSTP1, UGT1A1*28, and XRCC1).

Results: Forty-two patients enrolled between December 2001 and January 2004. Six patients achieved partial responses (14%), and 19 (45%) had stable disease. The median progression-free survival was 6.9 months. The median overall survival was 11.7 months, with 1-year overall survival of 42%. The most common toxicities were hematologic; grade 3 or 4 neutropenia was experienced by 26 patients (62%) during treatment, and 15 patients (36%) experienced grade 3 or 4 thrombocytopenia. The homozygous UGT1A1*28 (7/7) genotype was associated with grade 4 neutropenia in three of four patients (75%), but only eight out of 30 (27%) with 6/6 or 6/7 genotypes experienced grade 4 neutropenia ($p = 0.09$). None of the 14 patients with the GSTP1 I105V A/A genotype had a partial response, as opposed to five out of 19 (26%) of those with the G/A or G/G genotypes ($p = 0.057$).

Conclusion: The combination of carboplatin and irinotecan is an active combination in NSCLC, with response rates comparable with other platinum-containing doublets. Further studies with irinotecan should incorporate prospective pharmacogenomic analysis to identify markers for response and toxicity.

Key Words: Non-small cell lung cancer, Metastasis, Carboplatin, Irinotecan.

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There will be an estimated 172,570 new cases of lung cancer diagnosed in 2005, and an estimated 163,510 patients will die of lung cancer in the same year.[1] Cisplatin-based chemotherapy has been shown to lengthen survival time in these patients and improve quality of life.[2] Carboplatin-based regimens seem to provide clinically similar survival compared with cisplatin-containing regimens, but they may be associated with less morbidity.[3–5] Despite the recent advances, the overall survival for patients with metastatic NSCLC continues be poor, with 1-year survival less than 40%.[6,7]

Irinotecan (Camptosar) is a camptothecin-derived compound whose active metabolite, SN-38, interacts with topoisomerase I by stabilizing the complex formed with DNA.[8] In addition to this novel cytotoxic mechanism, irinotecan differs from other available chemotherapeutic agents in that multidrug-resistant cell lines retain sensitivity to irinotecan.[9] It has been approved for the treatment of metastatic colon cancer in the United States. As a single agent, the response rates in NSCLC vary from 15 to 34%.[10–13]

Preclinical studies suggest that irinotecan and platinum compounds act synergistically in vitro.[8] Response rates as high as 52% have been reported when irinotecan was combined with cisplatin in patients with previously untreated stage III B or IV NSCLC.[14] A randomized phase III study compared the efficacy of single-agent weekly irinotecan and weekly irinotecan administered with cisplatin with a regimen of cisplatin and vindesine.[13] The overall response rates for the three arms were 21, 44, and 32%, respectively, although there were no statistically significant differences between the arms.

Carboplatin in combination with weekly irinotecan has been shown to be tolerable in phase I studies, with dose-

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limiting toxicities of myelosuppression and diarrhea.[15] Subsequent phase II study of weekly administration demonstrated a response rate of 36% in patients with advanced NSCLC in a Japanese patient population.[16] A modified schedule delivering the irinotecan every 3 weeks rather than every week could potentially be more tolerable and convenient. Based on the phase I study demonstrating the feasibility of administering both irinotecan and carboplatin, we conducted a phase II study in advanced NSCLC.

There are no reliable molecular predictors of toxicity or response to therapy in NSCLC. Irinotecan is a prodrug (CPT-11) that is metabolized into its active form, SN-38, when inside the cell.[17] Irinotecan and SN-38 may be transported out of the cell via multidrug transporters such as ABCB1. Irinotecan is converted into SN-38 via human carboxylesterases[18] but can also be converted to inactive metabolites via CYP3A4 and CYP3A5, and SN-38 can be inactivated through glucuronidation to SN-38G via UGT1A1. The UGT1A1*28 allele provides the strongest support for a role of pharmacogenetics in predicting toxicity from irinotecan therapy.[19,20] There are few data on carboplatin pharmacogenetics, but polymorphisms in DNA repair and detoxification enzymes such as ERCC2, XRCC1, and glutathione S-transferase-Pi (GSTP1) have been associated with response to other platinum chemotherapy agents.[21–24]

To determine the impact of ABCB1, CYP3A4, ERCC2, GSTP1, UGT1A1, and XRCC1 polymorphisms on response or toxicities from irinotecan and carboplatin, we collected blood samples for pharmacogenetic analysis from consenting patients.

PATIENTS AND METHODS

Patient Selection

Adult (>18 years of age) patients were eligible who had histologically documented, unidimensionally measurable NSCLC with stage IIIB, IV, or recurrent disease. Patients with a controlled and treated brain metastasis were eligible. Patients could not have had prior chemotherapy for metastatic or advanced NSCLC. Prior irradiation was allowed, provided that at least 2 weeks had elapsed since the completion of therapy and the patients had a measurable lesion that had not been irradiated. Patients were required to have an ECOG performance status of 0 to 2 and a life expectancy of at least 3 months. Laboratory requirements included proof of adequate bone marrow function (absolute neutrophil count [ANC] $>1500/mm^3$ and platelet count $>100{,}000/mm^3$) and adequate liver (bilirubin $\leq 1.5 \times$ upper limit of normal) and renal function (creatinine ≤ 2.0 or calculated creatinine clearance of >60 mL/min if the creatinine was above 2.0). Computed tomographic scans of the affected areas (chest, abdomen, and/or pelvis) were required to have been done within 4 weeks of study entry. Patients were required to be free from uncontrolled intercurrent illness. Patients with active second malignancies (excluding nonmelanoma skin cancer) were not eligible, nor were patients using or having used phenytoin or carbamezepine within 7 days before enrollment, because these drugs have been associated with an increased metabolism of irinotecan. All patients signed informed consent before enrollment. The protocol was reviewed and approved by the institutional review board of Washington University School of Medicine.

Treatment and Patient Evaluation

Both irinotecan and carboplatin were administered intravenously every 3 weeks. The first five patients received irinotecan at a dose of 250 mg/m^2, but subsequent patients received irinotecan at a dose of 200 mg/m^2 because excessive dose delays for neutropenia had been noted with higher doses of irinotecan. Irinotecan was infused for 90 minutes, and then carboplatin was given for 1 hour at a target area under the concentration–time curve of 5. All patients received a 5-HT3 receptor antagonist before treatment for nausea prophylaxis. Atropine (0.5 mg intravenously) was given before irinotecan as prophylaxis against early cholinergic syndrome associated with this agent. Patients were instructed in the use of loperamide for treatment of diarrhea. Routine prophylactic use of G-CSF was not recommended.

Patients underwent weekly complete blood counts and a complete metabolic profile at the initiation of each course of chemotherapy. Patients also underwent physical examination and toxicity assessment before each cycle. Assessment of disease response was performed by computed tomographic scan every two cycles of chemotherapy (or sooner if clinically warranted). Patients could receive up to six cycles of therapy; they were removed from the study on disease progression or if they reached unacceptable toxicity (per protocol criteria or patient/physician opinion). Patients also left the study if they withdrew consent or in cases of treating physician or patient request or decline in health status precluding further therapy or follow-up.

Dose Modification

Toxicity was graded using the National Cancer Institute common toxicity criteria (version 2.0). No treatments could be administered unless all previous toxicities greater than or equal to grade 2 had resolved, ANC had returned to $>1500/mm^3$, and platelet count had returned to $>100{,}000/mm^3$. The dose of irinotecan was reduced by 20% if the patient's nadir ANC in the previous cycle had been $<500/mm^3$ for more than 7 days or if he or she had experienced febrile neutropenia. If the patient suffered a subsequent cycle with neutropenic fever or ANC $<500/mm^3$ for more than 7 days, filgrastim was allowed for subsequent cycles. If there was still ANC $<500/mm^3$ for more than 7 days or neutropenic fever in subsequent cycles, the patient was removed from study. The following modifications were made based on diarrhea: the previous cycle toxicity must have resolved to grade 1 or less (no more than three stools per day during pretreatment) before initiation of the next cycle. If a patient suffered grade 2 diarrhea (four to six stools during pretreatment), subsequent cycles dose of irinotecan was reduced by 15%. If a patient suffered grade 3 diarrhea (seven or more stools during pretreatment or a need for intravenous fluid support), in subsequent cycles dose of irinotecan was reduced by 25%. Diarrhea causing hemodynamic collapse (grade 4) was cause for removal from study. For all other nonhematologic toxicity, if a patient suffered grade 2 or 3 toxicity,

subsequent doses of irinotecan were reduced by 15%. If a patient suffered grade 4 nonhematologic toxicity (other than diarrhea), doses of irinotecan were reduced by 25% in subsequent cycles. Dose reescalation was not permitted in this study. Carboplatin dose was not modified for toxicities during this study.

Determination of Dose Intensity

Dose intensity, defined as the amount of drug delivered per unit of time,[25] was determined for both agents. The RDI for irinotecan was calculated based on a reference dose of 67 mg/m^2 per week (200 mg/m^2 per cycle), and the carboplatin Relative Dose Intensity (RDI) was based on the total weeks on therapy.

Response Evaluation

Response was evaluated by Response Evaluation Criteria in Solid Tumors criteria. Tumor reassessment was performed by the same imaging method used to establish a baseline at study entry. When there was disagreement regarding the exact measurement and response determination, a third-party radiologist reevaluated the computed tomographic scans for response. Time to response was defined as the time from the first day of therapy to the first observation of an objective response. Duration of response was defined as the time from the first observation of an objective response to the first observation of progressive disease. Duration of response was not calculated for those without response (those without stable disease [SD] or partial response [PR]). Time to tumor progression was defined as the time from the first day of therapy to the first observation of progressive disease. Overall survival was defined as the time from the first day of therapy to death, and progression-free survival was defined as the time from the first day of therapy to the date of documented progression or death (whichever occured first).

Pharmacogenomic Analysis

Blood samples were collected on consenting patients (n = 38) for pharmacogenetic analysis. Genomic DNA was extracted from 1 ml of whole blood using the Gentra PureGene Blood Kit (Gentra, Minneapolis, MN) following the manufacturers' instructions and was reconstituted in 10 mM Tris/1 mM EDTA (pH 7.6). Variations in the genes of interest (ABCB1 3435C>T [I1143I]; CYP3A4*1B [-392A>G]; ERCC2 2251 T>G [K751Q]; GSTP1 313A>G [I105V]; UGT1A1*28 [$(TA)_7$TAA]; XRCC1 1196G>A [R399Q]) were analyzed using polymerase chain reaction (PCR) and pyrosequencing. Analysis of the ABCB1, CYP3A4, ERCC2, and UGT1A1 variants was performed using PCR and pyrosequencing primers as previously described.[26–28] PCR primers for GSTP1 I105V (forward: 5′-Biotin-GGTGAATGACGGCGTGGA-3′; reverse: 5′-CCCTTTCTTTGTTCAGCCCC-3′) and XRCC1 R399Q (forward: 5′-Biotin-TAAGGAGTGGGTGCTGGACTGTC-3′; reverse: 5′-TGACTCCCCTCCAGATTCCT-3′) were designed using Primer Express version 1.5 (ABI, Foster City, CA). The pyrosequencing primers GSTP1 I105V: 5′-TTGGTGTAGATGAGGGA-3′ and XRCC1 R399Q 5′-GAGGCCTTACCT-3′ were designed using the pyrosequencing SNP Primer Design Version 1.01 software (*http://www.techsupport.pyrosequencing.com*). PCR was carried out using Amplitaq Gold PCR master mix (ABI, Foster City, CA), 5 pmole of each PCR primer, and 5 to 10 ng of DNA. Pyrosequencing was performed and analyzed as previously described[26] using a pyrosequencing PSQhs96A instrument and software (Biotage, Uppsala, Sweden).

Statistical Analysis

Data analysis of this study is mainly descriptive. The primary objective of the study was to determine the response rate for the combination of carboplatin and irinotecan when given every 3 weeks to patients with stage IIIB or IV NSCLC. Secondary objectives included determination of 1-year overall survival and progression-free survival and toxicity and evaluation of the influence of pharmacogenomic variation in the genes involved in irinotecan or carboplatin metabolism on toxicity. Kaplan-Meier curves were used to describe overall survival and progression-free survival, and Fisher's exact test was performed to explore the possible correlation between pharmacogenomic variation and toxicity/response.

RESULTS

Patient Demographics

Forty-two patients were enrolled between December 2001 and January 2004. The first five patients experienced excessive hematologic toxicity resulting in multiple treatment delays. Given this toxicity, the decision was made to reduce the irinotecan dose to 200 mg/m^2; this initial dose was given to the subsequent 37 patients. Table 1 summarizes the patient characteristics. Sixty-two percent were males, and median age was 60 years (range, 33–77). Adenocarcinoma was the

TABLE 1. Baseline Characteristics of Enrolled Population (n = 42)

	Total	
	n	**%**
Age		
Mean	60	
Range	33–77	
Gender		
Male	26	61.9
Female	16	38.1
Histologic subtype		
Adenocarcinoma	29	69
Squamous	4	10
Poorly differentiated NOS	6	14
Other	3	7
Stage at study entry		
IIIB	9	21
IV	29	69
Recurrent	4	10
Performance status		
0	11	26
1	28	67
2	3	7

TABLE 2. Cycles of Chemotherapy Delivered

Number of Cycles	Frequency	Percent of Total
1	10	23.8
2	7	16.7
3	1	2.4
4	6	14.3
5	1	2.4
6*	17	40.5
Total	160	100

*Includes one patient who received an additional two cycles off protocol, for a total of eight.

TABLE 3. Reasons for Patient Removal from Study in First Cycle

Patient	Reason for Removal from Study
1	Found to have new rectal cancer
2	Removed by treating physician because of decreased performance status
3	Given radiation for palliation of hemoptysis
4	Died of gram-negative sepsis*
5	Died of transfusion-associated lung injury
6	Removed for grade 4 diarrhea*
7	Removed for grade 4 diarrhea*
8	Removed for treatment delays caused by intercurrent myocardial infarction

*Treatment-related toxicity.

most common histology (69%). Most patients (79%) had metastatic or recurrent disease, with the remainder presenting as stage IIIB with malignant pleural effusion.

Drug Delivery

A total of 160 cycles were administered to the 42 patients (Table 2). One patient received an additional two cycles off protocol for a total of eight cycles, and one patient who was removed from the study per protocol after three cycles for treatment delay received a fourth cycle off protocol; these patients' toxicities from these off- protocol cycles are included in this analysis. Thirty-two patients received two or more cycles of chemotherapy, and 24 patients received four or more cycles of chemotherapy. The mean RDI of irinotecan and carboplatin were 91.2 and 92.2 percent, respectively. No significant association between the RDI of irinotecan and treatment response, progression-free survival, and overall survival was noted.

Efficacy

Of the 42 patients enrolled, eight patients (19%) were removed from study within the first cycle for reasons not related to disease progression (Table 3). The remaining 34 patients were evaluable for response. No patient had a complete response. Six patients achieved partial responses (14% of the total), whereas 19 (45%) had stable disease, with an average 47-day time to first response and 176-day duration of response. Nine patients developed progressive disease (21%) within the first two cycles.

Median follow- up time was 11.7 months. The median progression-free survival was 6.9 months (95% confidence interval (CI), 3.5–7.8), with a 1-year progression-free survival of 9.5%. The median overall survival was 11.7 months (95% CI, 8.4–13.2), with a 1-year overall survival of 42% (Fig. 1).

Toxicity

Grade 3 and 4 toxicities are presented in Table 4, listed as number of patients experiencing experiencing grade 3 or 4

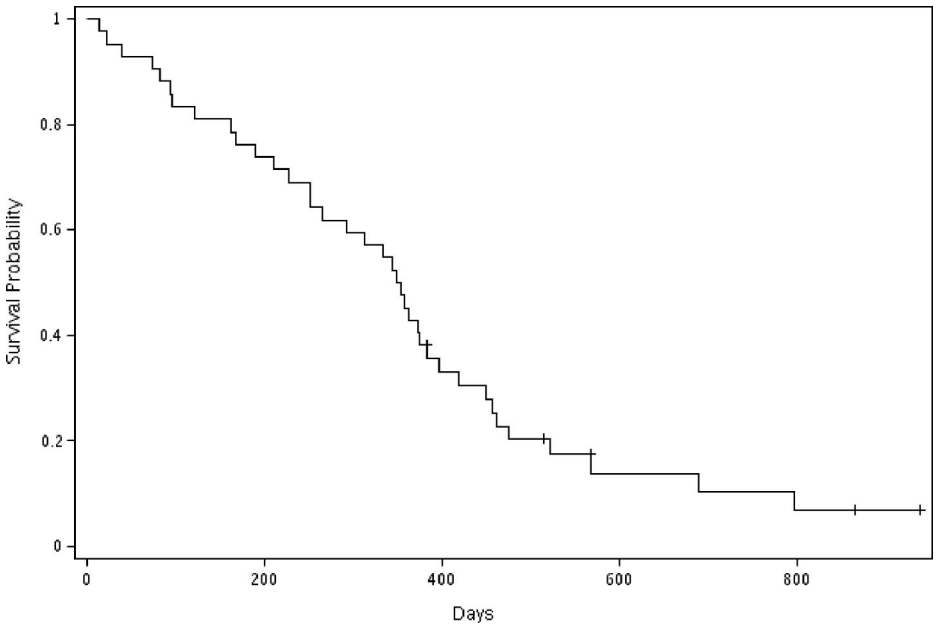

FIGURE 1. Overall survival.

TABLE 4. Common Toxicity Criteria (CTC) Grade 3 and 4 Toxicity

Patients Experiencing as Their Worst Toxicity				
	CTC Grade 3		CTC Grade 4	
Toxicity	No.	%	No.	%
Neutropenia	11	26	15	36
Thrombocytopenia	10	24	5	12
Anemia	9	21	1	2
Neutropenic fever			8	19
Diarrhea	2	5	3	7
Hyperglycemia	1	2		
Dizziness	4	10		
Dehydration	1	2		
Fatigue	1	2		
Nausea	5	12		
Emesis	2	5		
Malaise	2	5		
Pain	4	10		
Infection	3	7		
Dyspnea	7	17		

Hospitalizations occurred in 16 patients (38.1%), and phlebitis (DVT or PE) occurred in three patients (7.1%).

toxicities in any cycle as their worst toxicity. In the first cycle, one patient died of transfusion-related acute lung injury, which was considered unrelated to treatment, and one patient died of neutropenic sepsis and grade 4 diarrhea related to treatment. The most common toxicities were hematologic; grade 3 or 4 neutropenia was experienced by 26 patients (62%) at some point in their treatment course. A total of 15 patients (36%) experienced grade 3 or 4 thrombocytopenia as their worst toxicity. A total of 38 (of 160) cycles of delivered chemotherapy were complicated by grade 3 neutropenia (24%), and a total of 22 cycles (52%) were complicated by grade 4 neutropenia.

Pharmacogenomic Analysis

Pharmacogenetic data were available for 38/42 patients (Table 5). The homozygous UGT1A1*28 (7/7) genotype was associated with grade 4 neutropenia in three of four patients (75%), as opposed to eight of 30 (27%) in those with 6/6 or 6/7 genotypes, but this relationship failed to achieve statistical significance ($p = 0.09$). None of the 14 patients with the GSTP1 I105V A/A genotype had a partial response, as opposed to five out of 19 (26%) of those with the G/A or G/G genotypes, but this association did not reach statistical significance ($p = 0.057$). ABCB1 3435C>T, CYP3A4*1B, ERCC2 K751Q, and XRCC1 R399Q showed no significant association with grade 4 neutropenia or PR ($p > 0.05$). Given the relative rarity of other toxicities in this study, correlation between these alleles and other toxicities was not performed.

DISCUSSION

In this phase II study, the combination of irinotecan and carboplatin administered once every 3 weeks produced a 1-year survival rate similar to what has been reported with platinum doublets. Other investigators have also tested the combination of a platinum compound with irinotecan using various schemas (Table 6). None of these regimens seem to produce superior results. Nevertheless, toxicity profiles vary between these different regimens. It would be desirable to identify clinical or laboratory markers that would help identify patients at risk for therapy-related toxicities and those likely to respond to a given therapy.

We investigated multiple polymorphisms related to irinotecan metabolism, but we failed to demonstrate the association of any of these alleles with toxicity or response. We did find a trend toward a correlation between therapy-related severe neutropenia in patients homozygous for UGT1A1*28, although given the small number of patients in this association, it is difficult to draw firm conclusions. UGT1A1 is involved in the metabolism of the active metabolite of irinotecan (SN-38), detoxifying it by glucuronidation. The association of the UGT1A1*28 allele has been associated with risk of neutropenia with irinotecan by others[20,29] and is part of the basis for an FDA-approved test of UGT1A1 genotype and recent changes to the Camptosar package insert.[30,31] Additionally, the GSTP1 gene is involved with the detoxification of several chemotherapeutic agents, including platinum agents,[22,23] and its overexpression or overactivity is associated with chemoresponsiveness in several tumor types, including lung.[32] We have demonstrated a trend toward decreased response with the GSTP1 I105V A/A polymorphism, although this again failed to reach statistical significance. Our inability to uncover statistically significant associations between alleles studied and toxicity or response is most likely a reflection of the small number of data points that we were able to analyze in this optional portion of a study with a limited number of subjects.

TABLE 5. Genotype and Allele Frequencies for 38 Study Patients

Polymorphism	*n*	Homozygous Wild Type	Heterozygous	Homozygous Variant	*p*	q
ABCB1 3435C>T	34	9	11	14	0.43	0.57
CYP3A4*1B	38	26	7	5	0.78	0.22
GSTP I105V	33	14	14	5	0.64	0.36
ERCC2 K751Q	31	13	14	4	0.65	0.35
XRCC1 R399Q	33	18	13	2	0.74	0.26
UGT1A1*28	34	12	18	4	0.62	0.38

TABLE 6. Irinotecan/Platinum Doublet Regimens

Authors	*n*	Regimen	CR + PR Rate	1-year Survival	Grade 3/4 Toxicities
Masuda 1998[33]	70	Irinotecan 60 mg/m^2 days 1, 8, and 15 Cisplatin 80 mg/m^2 day 1 every 4 weeks	50%*	33%	Diarrhea 19% Neutropenia 80%
Mori 1999[34]	41	Irinotecan 160 mg/m^2 day 1 Cisplatin 20 mg/m^2/day 5-day continuous infusion G-CSF	59%	44%	Diarrhea 23% Neutropenia 20% Thrombocytopenia 15%
DeVore 1999[35]	52	Irinotecan 60 mg/m^2 days 1, 8, and 15 Cisplatin 80 mg/m^2 day 1 every 4 weeks	29%	37%	Diarrhea 17% Neutropenia 46%
Kakolyris 2001[36]	44	Irinotecan 100 mg/m^2 day 1 110 mg/m^2 day 8 Cisplatin 80 mg/m^2 day 8 every 3 weeks	22%	30%	Diarrhea 27% Neutropenia 46% Thrombocytopenia 9%
Jagasia 2001[37]	50	Irinotecan 65 mg/m^2 Cisplatin 30 mg/m^2 weekly, 4 out of 6 weeks	36%	46%	Diarrhea 26% Neutropenia 26% Thrombocytopenia 14%
Ueoka 2001[38]	44	Irinotecan 50 mg/m^2 days 1 and 8 Cisplatin 60 mg/m^2 days 1 and 8 every 4 weeks	48%*	57%	Diarrhea 25% Neutropenia 71%
Negoro 2003[13]	133†	Irinotecan 60 mg/m^{2}days 1, 8, and 15 Cisplatin 80 mg/m^2 day 1 Every 4 weeks	44%	47%	Diarrhea‡ 12% Neutropenia‡ 37% Thrombocytopenia 3%
Takeda 2002[39]	36	Irinotecan 50 mg/m^2 days 1, 8, and 15 Carboplatin AUC 5 day 1 Every 4 weeks	25%	42.2%	Diarrhea 6% Neutropenia 77% Thrombocytopenia 47%
Cardenal 2003[40]	73	Irinotecan 200 mg/m^2 day 1 Cisplatin 80 mg/m^2 day 1 every 3 weeks	34.2%	31%	Diarrhea 29% Febrile neutropenia 14%
Fukuda 2004[16]	61	Irinotecan 50 mg/m^2 days 1, 8, and 15 Carboplatin AUC 5 day 1 Every 4 weeks	34%	38%	Diarrhea 7% Neutropenia 60% Thrombocytopenia 25%
Georgoulias 2005[41]	74§	Irinotecan 110 mg/m^2 day 1 100 mg/m^2 day 8 Cisplatin 80 mg/m^2 day 8 every 3 weeks	23%	34%	Diarrhea 27% Neutropenia 31% Thrombocytopenia 7%

AUC, area under the curve.
*Of evaluable patients (not of the total).
‡As part of a phase III randomized trial between irinotecan/cisplatin, irinotecan alone, and vindesine/cisplatin.
‡Grade 4 toxicity only.
§As part of a randomized phase II trial.

Clearly, an efficacy plateau has been reached using doublet therapy with traditional chemotherapy agents in NSCLC. Multiple regimens are available with comparable therapeutic efficacy but differing toxicity profiles. Future studies should focus on the genetic basis for predictors of response and toxicity in individual patients, possibly by mandatory collection of genomic material at study entry to discover more statistically robust associations. This approach holds the promise of tailoring drugs to patients to avoid therapies that would produce excess toxicity and, possibly, steering individual patients to the most effective available therapy.

CONCLUSION

The combination of irinotecan and carboplatin in this phase II study produced median and 1-year survival rates similar to the results obtained with other platinum-based doublets. Nevertheless, this regimen was associated with a fairly significant degree of neutropenia (including febrile neutropenia), although incidence of severe diarrhea was lower than that reported with weekly irinotecan infusion. Correlative pharmacogenomic analyses suggest possible relationships between UGT1A1*28 and toxicity and GSTP1 I105V and response, but these relationships failed to reach statistical significance, likely because of the small sample size. Further studies with irinotecan should incorporate prospective pharmacogenomic analysis to identify selective markers for response and toxicity.

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