The Role of Irinotecan in Non-Small Cell and Small-Cell Lung Cancer

Die Rolle von Irinotecan bei nicht-kleinzelligem und kleinzelligem Bronchialkarzinom

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Introduction

There were 120,000 deaths from non-small cell lung cancer (NSCLC) in the United States last year. At least one half of patients with NSCLC present with stage IIIB or IV disease. With the current platinum-containing doublets and some non-platinum doublets the 1-year survival of these patients is 35–45%, the median survival is 8–10 months, and the 5-year survival is between 5 and 10%.

One of the promising approaches to improve the outcome for patients with advanced NSCLC is the incorporation of new agents such as irinotecan, a topoisomerase I inhibitor which is active in a broad spectrum of tumor types and has been licensed in the US for the treatment of advanced colorectal carcinoma.

Single Agent and Combination in First-Line Therapy

Four phase II studies with single-agent irinotecan in first-line therapy of advanced NSCLC have been completed (table 1). Response rates in these studies ranged from 15–35% and demonstrated significant activity of irinotecan in NSCLC. A logical next step in the development of irinotecan in NSCLC was to design regimens which combine irinotecan with other active agents with non overlapping toxicities. The drugs that have been evaluated most extensively in this setting are the platinum analogs and the taxanes.

Three phase II studies with the combination of irinotecan/platinum as first-line therapy in advanced NSCLC have been completed (table 2). The response rates ranged from 29 to 52%

Table 1. First-line irinotecan for advanced NSCLC, irinotecan single-agent efficacy (mod. after Denes)

Author	Regimen mg/m ² weekly	Response rate %	Time to progression median	Overall survival median
Negoro, 1991	100	34	n.r.	n.r.
Fukuoka, 1992	100	32	15 weeks	42 weeks
Douillard, 1995	350 q3	36	n.r.	n.r.
Baker, 1997	100×4 q6	15	2.8 months	6.2 month

n.r. = Not reported.

Table 2. First-line irinotecan for advanced NSCLC, irinotecan combination regimes (mod. after Denes)

Regimen irinotecan+	Country	N	Response rate %	Overall survival months (median)
Cisplatin	Japan	70	52	10.2
Cisplatin	USA	52	29	9.9
Cisplatin	USA	45	42	10.8
CBDCA+paclitaxel	USA	31	65	n.a.

n.a. = Not available.

Table 3. First-line irinotecan + cisplatin: phase III efficacy (mod. after Masuda et al. [3])

Regimen irinotecan+	Response rate %	Overall survival weeks (median)		1-Year overall survival %
		IIIB	IV	
Cisplatin	43*	51.7	53.9**	48.5
VDS	31	47.1	37.9	39.9
21	47.4	42.1	43.5	

* p < 0.001; ** p = 0.004.

Table 4. First-line irinotecan + cisplatin for advanced NSCLC: phase III toxicities¹ (mod. after Masuda et al. [3])

Grade 3/4 toxicities	Irinotecan + Cisplatin	Cisplatin + VDS	Irinotecan
<i>Hematologic</i>			
Leukopenia	40.2*	51.6	11.0
Neutropenia	70.9	82.3	25.2
Anemia	31.5	19.4	7.1
Platelets	7.1	3.2	0.0
<i>Nonhematologic</i>			
Nausea/Vomiting	32.3	22.6	9.4
Diarrhea			
Grade 3	9.5	2.4	10.3
Grade 4	3.1	1.6	4.7

¹ All values in percent.

Table 5. Single agent irinotecan for second-line SCLC: phase II response rates (mod. after Denes)

Author	N		Response rate, %	
	sensitive	refractory	sensitive	refractory
Negoro, 1991	27 ¹		33	
Masuda, 1992	5	10	47 ²	11.0
Le Chevalier, 1997	32	0	16	0
DeVoro, 1998	17	27	29	4 ³

¹ Sensitive or refractory.

² Including 2 complete responses.

³ Including 1 complete response.

and the median survival was found to be in excess of 10 months by 2 investigators. Following these excellent results Masuda et al. [1] conducted a large phase III trial in Japan. Almost 400 patients with advanced, previously untreated patients with stages IIIB and IV disease were randomized to 1 of 3 arms: cisplatin/irinotecan, cisplatin/vindesine, and irinotecan as a single agent. The best response rate (43%) and 1-year survival (48.5%) was in the group receiving cisplatin/irinotecan. This regimen produced a median survival of 53.9 weeks in patients with stage IV disease. A remarkable finding was the survival of patients receiving single agent irinotecan (table 3). Toxicity was substantial with both combination regimens (table 4).

In the United States DeVore and coworkers conducted two sequential phase II studies using the combination of irinotecan and platinum. The first trial used the same dose and schedule as Masuda [2], but reported inferior results with a response rate of 29% and 1-year survival of 27% and substantial toxicity. The second trial attempted to reduce toxicity. This regimen was less toxic and the dose intensity of irinotecan was maintained in 89% of patients. The response rate was 39% with a 1-year survival of 45%. This regimen is currently being evaluated in a phase III study.

Conclusions for NSCLC

The activity of a monthly irinotecan/cisplatin regimen is comparable to other commonly used platinum-based doublets. In one trial, a highly significant survival advantage was seen with irinotecan/cisplatin in patients with stage IV disease. Weekly irinotecan/cisplatin regimens appear to be more active and better tolerated than monthly schedules. Studies incorporating thoracic radiation are clearly warranted.

The Role of Irinotecan in Small Cell Lung Cancer

Small cell lung cancer (SCLC) remains a major health problem in the United States with approximately 40,000 deaths last year. Current treatment approaches yield initial complete response rates of 45–75% in patients with limited disease and 20–30% in patients with extensive stage at diagnosis.

Initial Response Does Not Translate Into Long-Term Survival

Currently, the median survival of patients with limited disease is 18 months compared to only 9 months in patients with extensive stage at diagnosis. Long-term survival is only seen in patients with limited disease in whom less than 20% are alive 5 years after diagnosis. Unfortunately, these results have not improved substantially in the past 20 years.

From Second- to First-Line Therapy

New agents, such as irinotecan, which became available in the last decade have been evaluated in an attempt to improve the long-term results (table 5). Irinotecan has been evaluated in four phase II studies as second line therapy in SCLC. A substantial response rate of 47% was reported in an early study for Japan [3]. DeVore and colleagues have confirmed much higher response rates in patients with sensitive relapse compared to refractory relapse.

Irinotecan is active with manageable toxicities as second-line therapy in SCLC. These results suggested that irinotecan may be more active in first-line therapy, particularly when combined with other active agents.

Table 6. Irinotecan for first-line SCLC: irinotecan-based combination regimens (mod. after Denes)

Author	Regimen irinotecan +	Limited disease N	Extended disease N	Response rate, %		Median survival months
				complete	overall	
Kudoh, 1998	cisplatin	40	–	30	83	14.3
		–	35	29	86	13.0
Sugiura, 1998	CBDCA	13	–	15	77	n.a.
		–	3	0	67	n.a.
Sekine, 1998	cisplatin+VP-16	10 ¹		20	100	n.a.
Nakamura, 1999	VP-16	0	50	10	66	12

¹ Limited and extended disease.

Table 7. First-line irinotecan + cisplatin for SCLC: response rates (mod. after Kudoh et al. [5])

Disease	Response rate %	Complete response %	Partial response %	Overall survival median, months	2-Year survival %
Limited	83	30	52	14.3	17.5
Extended	86	29	57	13.0	21.7

Low Survival Rates in Limited Disease

The study by Kudoh and coworkers [5] included 40 patients with limited and 35 patients with extensive disease (table 6). Irinotecan was given on days 1, 8, and 15 at a dose of 60 mg/m² and cisplatin was given on day at 60 mg/m². Treatment was repeated on day 29 of each cycle. Patients with limited disease who achieved complete (CR) or partial remission (PR) after 4 cycles of chemotherapy were given 50 Gy thoracic radiation. Complete responders also received prophylactic cranial irradiation. Patients with extensive disease were given a maximum of 6 cycles of chemotherapy. The toxicity of this regimen was substantial: grade 3/4 hematologic toxicities included neutropenia (77%) and anemia (39%); 25% of patients required transfusions. Nausea was the leading non-hematologic toxicity (35%) followed by diarrhea (19%). Interestingly, the response rates were similar in limited and extensive-disease patients (table 7), but survival was disappointing in limited disease patients. Two possible reasons for the low survival in limited disease are: A) significant dose reduction because of toxicity

(neutropenia and diarrhea), and B) only 20 of 24 patients received their planned radiation.

A phase III evaluation of this regimen and a standard regimen of VP-16/platinum has been completed. The response rates have not been published, however the toxicity profile was unacceptable and led to a modification of the schedule to omit the day-15 dose of irinotecan and to administer cisplatin at 30 mg/m² on a day-1, day-8 schedule every 3 weeks. This regimen is now being evaluated in the phase III setting.

Conclusion for SCLC

The combination of irinotecan and cisplatin has significant activity in SCLC, particularly in patients with extensive-stage disease. The current regimens are associated with hematologic and gastrointestinal toxicity and additional schedules are being explored. Further evaluation of irinotecan with non-platinum regimens and with radiation is warranted.

References

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