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Irinotecan in cancers of the lung and cervix

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Irinotecan is active as a single agent in advanced non-small cell lung cancer (NSCLC), with overall response rates (ORRs) of 13–32% reported in phase II trials. In the first-line treatment of stage IIIB/IV NSCLC, phase II studies have suggested that the combination of irinotecan with cisplatin can achieve response rates of 29–75%, which is greater than achieved with older platinum-containing combinations. Neutropenia and diarrhea are the dose-limiting toxicities. In small cell lung cancer (SCLC), irinotecan alone has achieved ORRs of 16–47% in previously treated SCLC, which is higher than expected with oral etoposide. Studies with irinotecan in combination with cisplatin or etoposide have reported responses of up to 79%. Irinotecan is active in cervical cancer patients whose metastases are outside the area of previous irradiation (ORR 24%) and a major phase II/III study is currently comparing irinotecan as single agent or in combination with cisplatin against a reference cisplatin arm. [© 1999 Lippincott Williams & Wilkins.]

Key words: Cervical cancer, irinotecan, lung cancer.

Non-small cell lung cancer (NSCLC)

Approximately 40% of patients with NSCLC present with overt metastatic disease.[1,2] Untreated, the median survival for such patients is in the region of 4–6 months; with a low 1-year survival of 10%. Prior to 1995, the results obtained in multicenter trials of various cisplatin-based drug combinations were broadly similar: the overall response rates (ORRs) were 20–30%, the median survival 6–8 months and the chance of 1-year survival 20–25%.[3]

More recently, studies have suggested that these results can be matched by certain of the newer agents used as monotherapy (Table 1).[4–23] With the exception of topotecan, these newer agents have achieved response rates in the region of 20% when used as a first-line treatment.

Irinotecan, a topoisomerase I inhibitor, will be discussed in more detail. Three studies of this drug in first-line NSCLC are of particular interest. All used the standard dose of 100 mg/m^2, although the number of consecutive weeks on which irinotecan was administered varied. Negoro *et al.* studied 67 patients who received irinotecan weekly for 3 out of 4 weeks.[4] A response rate of 34% was reported. Fukuoka *et al.*[5] administered irinotecan weekly to 72 patients, achieving an ORR of 32%. The median survival for the 48 patients treated with irinotecan on a 4 out of 6 weeks cycle was 10.5 months.[5] Baker *et al.*[6] report an ORR of 16% and median 6.2 month survival.

These studies illustrated the potential enhanced activity of irinotecan in advanced NSCLC. The next logical step was to attempt to combine irinotecan with cisplatin, an active agent with known activity in NSCLC. Studies have demonstrated *in vitro* synergy between irinotecan and cisplatin in NSCLC cell lines both when cisplatin was administered before the active metabolite of irinotecan (SN 38) and when the agents were administered in reverse order.[24,25] Such consideration resulted in extensive clinical study of the combination (Table 2).[26–29]

Among the studies of the irinotecan/cisplatin combination, Masuda *et al.*[26] administered irinotecan 30–70 mg/m^2 on days 1, 8 and 15, together with cisplatin 80 mg/m^2 on day 1 every 4

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Table 1. First-line treatment of stage III/IV non-small cell lung cancer (NSCLC) using newer agents[4–23]

Agent	Response rate [% (range)]	Median survival (months)
Irinotecan[4–6]	16 (13–32)	6–10
Topotecan[7,8]	11 (4–24)	7–10
Docetaxel[9–13]	29 (21–38)	6–12
Paclitaxel[14,15]	25 (10–38)	6–10
Vinorelbine[16–18] *	16 (14–29)	7–8
Gemcitabine[19–23] *	22 (20–27)	7–9

*Includes phase III trials.

weeks. The dose-limiting toxicities (DLTs) were leukopenia and diarrhea, and the doses recommended for further studies were 70 mg/m^2 irinotecan plus 80 mg/m^2 cisplatin. A response rate of 54% was reported in 27 patients. Nakagawa *et al.*[27] administered cisplatin at the same dose plus irinotecan at a dose of 60 mg/m^2 on days 1, 8, and 15 every 4 weeks. In this study a 48% ORR in 69 patients was observed.[27] De Vore *et al.*,[28] using the same dose and schedule as Nakagawa, reported grade 3/4 neutropenia in 46% of patients and grade 3/4 diarrhea in 17%. The ORR was 31% in 52 patients.[28] Mori *et al.*[29] administered 160 mg/m^2 irinotecan on day 1 with cisplatin 20 mg/m^2 on days 1–5, every 4 weeks, supported by granulocyte colony stimulating factor (G-CSF). Myelosuppression and diarrhea were again the major toxicities. The ORR in 41 patients was 55%.[29]

Other combinations are been investigated with irinotecan in NSCLC. In ongoing or planned phase I trials, irinotecan will be administered in combination with a taxane (either docetaxel or paclitaxel), gemcitabine, mitomycin C or vinorelbine.

Small cell lung cancer (SCLC)

SCLC is a more chemosensitive tumor; response rates to the newer agents are again comparable to the more established chemotherapeutic agents.

There have been four trials of irinotecan in patients with previously treated SCLC. Negoro *et al.*[30] administered 100 mg/m^2 weekly irinotecan to 27 patients, reporting a response rate of 33%. Masuda *et al.*[31] delivered the same dose of drug weekly for 4 of 6 weeks to 15 patients, with an ORR of 47%. Le Chevalier *et al.*[32] took a different approach, using a 150 mg/m^2 per every other week schedule, which resulted in the lower ORR of 16% in 31 patients; and De Vore *et al.*[33] found the same response rate using 125 mg/m^2 irinotecan weekly for 4 of 6 weeks in 44 patients. Overall, these response rates are encouraging in pre-treated SCLC given that the response rate to standard treatment with oral etoposide would be around 20%.

Three studies have evaluated irinotecan in combination with other agents: all involved irinotecan delivered on days 1, 8 and 15 of a 28-day cycle. Okishio *et al.*[34] combined irinotecan 60 mg/m^2 with 60 mg/m^2 cisplatin, delivered on day 1, in 16 pre-treated patients, reporting an ORR of 19%. Fujiwara *et al.*[35] administered the same dose of cisplatin and 60–80 mg/m^2 irinotecan, finding an ORR of 79% in chemotherapy-naive patients. Masuda *et al.*[36] reported a response rate of 71% in 25 patients who had received prior chemotherapy, where 70 mg/m^2 irinotecan was combined with etoposide 80 mg/m^2 delivered on days 1–3.

Cancer of the cervix

In the US alone, there are 15 000 new cases each year of cervical cancer and 4600 deaths caused by

Table 2. First-line combination of platinum with irinotecan in stage III/IV non-small cell lung cancer (NSCLC)[26–29]

Author	Schedule and dose (mg/m^2)	No. of patients	ORR (%)
Masuda[26]	Irinotecan (30–70) day 1, 8 and 15 Cisplatin (80) day 1 Every 4 weeks	27	54
Nakagawa[27]	Irinotecan (60) day 1, 8 and 15 Cisplatin (80) day 1 Every 4 weeks	69	48
De Vore[28]	Irinotecan (60) day 1, 8 and 15 Cisplatin (80) day 1 Every 4 weeks	52	31
Mori[29]	Irinotecan (160) day 1 Cisplatin (20) days 1–5 Granulocyte colony stimulating factor Every 4 weeks	41	55

Table 3. New agents in the treatment of cervical cancer[39–45]

Author	Agent	No. of patients	Prior RT	Prior CT	ORR (%)	Duration of response	Survival
Morris[39]	Vinorelbine (30 mg/m² q weeks)	35	yes	no	18	5.2 months	11.0 months
Kudelka[40]	Paclitaxel + G-CSF (250 mg/m²/3 h q 3 weeks)	32	yes	no	25	2.0 months	7.3 months
McGuire[41]	Paclitaxel (135–170 mg/m²/24 h)	55	yes	no	17	3.4 months	–
Verschraegen[42]	Irinotecan (125 mg/m²/weekly, 4/6 weeks)	42	yes	yes	21	3.0 months	6.4 months
Takeuchi[43]	Irinotecan (150 mg/m² q 2 weeks or 100 mg/m² weekly)	69	yes	yes or no	24	75 days	9.0 months
Irvin[44]	Irinotecan (125 mg/m² × 4 q 6 weeks)	16	yes	yes	0	–	–
Sugiyama[45]	Irinotecan (60 mg/m² days 1, 8 and 15) + cisplatin (60 mg/m² day 1)	29	yes or no	no	65	–	–

RT, radiotherapy; CT, chemotherapy; ORR, overall response rate; G-CSF, granulocyte colony stimulating factor.

the disease.[37] In Europe, the incidence is 18 per 100 000 women, making cervical cancer the fourth most frequent female cancer. At diagnosis, 35–60% of cases are locally advanced or metastatic. Overall, the median 5-year survival is 58%. This figure rises to 75–90% in stage IB or IIA disease treated with surgery or radiotherapy alone. However, in stage IV disease or disease which recurs after radiotherapy, prognosis is poor and has shown no improvement in survival over the past 30 years.[38]

At least 19 drugs have been tested as single agents in the treatment of cervical cancer, with an ORR in the region of 15%.[38] In randomized studies, no combination regimen has been shown superior to single-agent cisplatin.[38] Monotherapy with cisplatin therefore remains the reference treatment in advanced or recurrent carcinoma of the cervix. At the optimal dose of 50–100 mg/m² every 3 weeks, the response rate is 20–40% (depending on performance status and prior irradiation), the median duration of response is 4 months and the median survival is 9 months.

There is a clear need for new agents in the treatment of this disease. Three new agents (vinorelbine, paclitaxel and irinotecan) have been systematically investigated (Table 3).[39–45]

Response rates with single-agent irinotecan have ranged from 0 (at a relatively low dose) to 24%.[42–44] In combination with cisplatin, an ORR of 65% was found in 29 patients.[45]

In the phase II EORTC/ECSG[46,47] study conducted between 1993 and 1996, a total of 51 evaluable patients were treated with 350 mg/m² irinotecan administered as a 30 min i.v. infusion every 3 weeks. The median age of the group was 47 years (range 30–71) and all but four patients were of performance status 0 or 1. A total of 211 cycles of treatment were given.

Although no patients had received prior chemotherapy, all but two had received prior radiotherapy. Patients were divided into two groups according to whether or not the target lesion was outside the irradiated area (37 patients enrolled) or inside the area (18 patients enrolled). The 34 patients evaluable for response whose lesion was outside the irradiated area received a median of four cycles of irinotecan (range 1–10). One complete response and seven partial responses were seen, giving an ORR of 24%. The median duration of response was 7.3 months, the time to progression was 4 months and overall survival was 8.2 months. However, in the second group of 17 evaluable patients with target lesions within the irradiated field there were no responses, despite a median of three cycles administered (range 1–7). The median time to progression in this group was 2.5 months and survival 4.2 months.

The treatment overall was well tolerated, with a median relative dose intensity of 0.97 (range 0.67–1.03). The principal toxicities were neutropenia and diarrhea.

It therefore seems that irinotecan is active in the subgroup of patients (with no prior chemotherapy) whose target lesions lie outside previously irradiated areas. However, local recurrences in previously irradiated fields are unresponsive to

irinotecan and such patients are at risk of toxicity (delayed diarrhea and neutropenia). The dose of drug administered should be adapted to take prior external radiation into account.

In an ongoing randomized phase II/III study involving centers in 18 countries, patients with relapses outside the irradiated field are being randomized to one of three treatment arms: irinotecan alone (350 mg/m^2 when no previous radiotherapy has been given, otherwise a dose of 250 mg/m^2 is administered), irinotecan (200 mg/m^2 or 160 mg/m^2) plus cisplatin 80 mg/m^2 and a reference arm of cisplatin 80 mg/m^2 alone. All treatments are given every 3 weeks. An interim analysis will be conducted once 29 patients have been treated in each arm. The better of the two investigational arms (irinotecan alone or irinotecan plus cisplatin) will then be compared with cisplatin alone in a further 228 patients.

In the initial phase II portion of the study, the primary endpoint is progression-free survival, with response rate, tolerability, response duration, time to treatment failure and survival as secondary endpoints. Survival will be the primary endpoint of the follow-on phase III part of the trial and secondary endpoints include quality of life. To date, in the initial 3 months of the study, 18 patients have been enrolled and 17 treated.

Discussion

Irinotecan is clearly active in both NSCLC and SCLC. In NSCLC, irinotecan combined with cisplatin results in ORRs of 29–75% which match or exceed those seen previously with platinum combinations.[26–29] Consistent results have been reported using weekly doses of 60–80 mg/m^2 irinotecan and 60–80 mg/m^2 cisplatin. Phase I/II studies in which irinotecan is combined with other active novel agents are underway. However, the efficacy of these combinations with irinotecan, relative to cisplatin-based combinations, will require phase III trial. Phase III trials are also warranted in SCLC, a disease in which irinotecan has demonstrated activity comparable with other new drugs both when used as a single agent and in combination with cisplatin.

Irinotecan has also shown activity in advanced cervical cancer and may have a helpful role either alone or in combination with the reference treatment, cisplatin. A phase II/III study is currently ongoing which will define the role of irinotecan in the treatment of cervical cancer.

References

1. Landis SH, Murray T, Bolden S, *et al.* Cancer statistics. *CA Cancer J Clin* 1999; **49**: 8–31.
2. Walling J. Chemotherapy for advanced non-small cell lung cancer. *Resp Med* 1994; **88**: 649–57.
3. Ginsberg JK, Kris MG, Armstrong JG. Cancer of the lung: non-small cell lung cancer. In: De Vita V, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology*. Philadelphia, PA: Lippincott 1993; **1**: 673–723.
4. Negoro S, Fukuoka M, Niitani H, *et al.* A phase II study of CPT-11, a camptothecin derivative, in patients with primary lung cancer. *Jpn J Cancer Chemother* 1991; **18**: 1013–9.
5. Fukuoka M, Niitani H, Suzuki A, *et al.* A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small cell lung cancer. *J Clin Oncol* 1992; **10**: 16–20.
6. Baker L, Khan R, Lynch T, *et al.* Phase II study of irinotecan in advanced non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1997; **16**: 461a (abstr 1658).
7. Kindler HL, Kris MG, Smith IE, *et al.* Phase II trial of topotecan administered as a 21-day continuous infusion in previously untreated patients with stage IIIB and IV non-small cell lung cancer. *Am J Clin Oncol* 1998; **21**: 438–41.
8. Lynch TJ, Kalish L, Straus G, *et al.* Phase II study of topotecan in metastatic non-small-cell lung cancer. *J Clin Oncol* 1994; **12**: 347–52.
9. Francis P, Rigas JR, Kris MG, *et al.* Phase II trial of docetaxel in patients with stage III and IV non-small-cell lung cancer. *J Clin Oncol* 1994; **12**: 1232–7.
10. Cerny T, Kaplan S, Pavlidis N, *et al.* Docetaxel (Taxotere) is active in non small cell lung cancer: a phase II trial of the EORTC Early Clinical Trials Group (ECTG). *Br J Cancer* 1994; **70**: 384–7.
11. Burris H, Eckardt J, Fields S, *et al.* Phase II trials of Taxotere with non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1993; **12**: 335 (abstr 1116).
12. Fossella FV, Lee JS, Berille J, *et al.* Summary of phase II data of docetaxel (Taxotere), an active agent in the first- and second-line treatment of advanced non-small cell lung cancer. *Semin Oncol* 1995; **22**: 22–9.
13. Robinet G, Kleisbauer JP, Thomas P, *et al.* Phase II study of docetaxel (Taxotere) in first- and second-line NSCLC. *Proc Am Soc Clin Oncol* 1997; **16**: 480 (abstr 1726).
14. Murphy WK, Fossella FV, Winn RJ, *et al.* Phase II study of Taxol in patients with untreated advanced non-small-cell lung cancer. *J Natl Cancer Inst* 1993; **85**: 384–8.
15. Chang AY. Non-small cell lung cancer. In McGuire WP, Rowinsky EK, eds. *Paclitaxel in cancer treatment*. New York: Marcel Dekker 1995: 273–9.
16. Depierre A, Lemaire E, Dabouis G, *et al.* A phase II study of navelbine (Vinorelbine) in the treatment of non-small-cell lung cancer. *American Journal of Clinical Oncology* 1991; **14**: 115–9.
17. Le Chevalier T, Brisgand D, Douillard JY, *et al.* Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994; **12**: 360–7.
18. Le Chevalier T, Pujol JL, Douillard JY, *et al.* Six year follow up of the European Multicenter Randomised Study comparing Navelbine (NVB) alone vs NVB + Cisplatin (CDDP) vs Vindesine (VDS) + CDDP in 612 patients with advanced non-small cell lung cancer (NSCLC). *Lung Cancer* 1997; **18**: 13 (abstr 39) (suppl 1).

19. Gatzemeier U, Shepherd FA, Le Chevalier T, *et al.* Activity of gemcitabine in patients with non-small cell lung cancer. *Eur J Cancer* 1996; **32**A: 243–8.
20. Anderson H, Lund B, Bach F, *et al.* Single-agent activity of weekly gemcitabine in advanced non-small-cell lung. *J Clin Oncol* 1994; **12**: 1821–6.
21. Le Chevalier T, Gottfried M, Gatzemeier U, *et al.* Confirmatory activity of gemcitabine in non small cell lung cancer (NSCLC). *Eur J Cancer* 1993; **29**A: S160 (suppl 6).
22. Anderson H, Cottier B, Nicolson M, *et al.* Phase III study of gemcitabine (Gemzar) versus best supportive care (BSC) in advanced non-small cell lung cancer (NSCLC). *Lung Cancer* 1997; **18**: 9 (abstr 24) (suppl 1).
23. Manegold Ch, Stahel R, Mattson K, *et al.* Single agent Gemzar (Gemcitabine, GEM) versus cisplatin plus etoposide (C/E): A randomized phase II study in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). *Lung Cancer* 1997; **18**: 11 (abstr 32) (suppl 1).
24. Kudoh S, Takada M, Masuda N, *et al.* Enhanced antitumor efficacy of the combination of CPT-11, a new derivative of camptothecin, and cisplatin against human lung tumor xenografts. *Jpn J Cancer Res* 1993; **84**: 203–7.
25. Kuraishi Y, Sano M, Hirano A, *et al. In vitro* combination effect of CPT-11, a new camptothecin derivative, in human non-small cell lung cancer cell lines. *Proc Am Soc Clin Oncol* 1992; **11**: 122 (abstr 308).
26. Masuda N, Fukuoka M, Kudoh S, *et al.* Phase I and pharmacological study of irinotecan in combination with cisplatin for advanced lung cancer. *Br J Cancer* 1993; **68**: 777–82.
27. Nakagawa K, Fukuoka M, Niitani H. Phase II study of irinotecan (CPT-11) and cisplatin in patients with advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1993; **12**: 1104 (abstr).
28. De Vore R, Crawford J, Dimery I, *et al.* Phase II trial of irinotecan (CPT-11) plus cisplatin (CDDP) in advanced NSCLC. *Proc Am Soc Clin Oncol* 1997; **16**: 466a (abstr 1674).
29. Mori K, Hirose T, Machida S, *et al.* A phase I trial of irinotecan and infusional cisplatin with recombinant human granulocyte colony-stimulating factor support in the treatment of advanced non-small cell lung cancer. *Eur J Cancer* 1997; **33**: 503–5.
30. Negoro S, Fukuoka M, Niitani H, *et al.* A phase II study of CPT-11, a camptothecin derivative, in patients with primary lung cancer. *Jpn J Cancer Chemother* 1991; **18**: 1013–9.
31. Masuda N, Fukuoka M, Kusunoki Y, *et al.* CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol* 1992; **10**: 1225–9.
32. Le Chevalier T, Ibrahim N, Chomy P, *et al.* A phase II study of irinotecan (CPT-11) in patients (pts) with small-cell lung cancer (SCLC) progressing after initial response to first-line chemotherapy (CT). *Proc Am Soc Clin Oncol* 1997; **16**: 450a (abstr).
33. De Vore RF, Blanke CD, Nenham CA, *et al.* Phase II study of irinotecan (CPT-11) in patients with previously treated small-cell lung cancer (SCLC). *Proc Am Soc Clin Oncol* 1998; **17**: 451a (abstr 1736).
34. Okishio K, Furuse F, Kawahara M, *et al.* A phase II study of irinotecan (CPT-11) and cisplatin (CDDP) in previously treated small cell lung cancer (SCLC). *Proc Am Soc Clin Oncol* 1998; **17**: 497a (abstr 1914).
35. Fujiwara Y, Yamakido M, Fukuoka M, *et al.* Phase II study of irinotecan (CPT-11) and cisplatin (CDDP) in patients with small-cell lung cancer (SCLC). *Proc Am Soc Clin Oncol* 1994; **13**: 335 (abstr 1110).
36. Masuda N, Matsui K, Negoro S, *et al.* Combination of irinotecan and etoposide for treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol* 1998; **16**: 3329–34.
37. Wingo PA, Tong T, Bolden S. Cancer statistics. *CA* 1995; **45**: 8.
38. Eifel PJ, Berek JS, Thigpen JT. Cancer of the cervix, vagina, and vulva. In: De Vita V, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology.* Philadelphia, PA: Lippincott 1993; **1**: 1433–78.
39. Morris M, Brader KR, Levenback C, *et al.* Phase II study of vinorelbine in advanced and recurrent squamous cell carcinoma of the cervix. *J Clin Oncol* 1998; **16**: 1094–8.
40. Kudelka AP, Winn R, Edwards CL, *et al.* An update of a phase II study of paclitaxel in advanced or recurrent squamous cell cancer of the cervix. *Anti-Cancer Drugs* 1997; **8**: 657–61.
41. McGuire WP, Blessing JA, Moore D, *et al.* Paclitaxel has moderate activity in squamous cervix cancer. *J Clin Oncol* 1996; **14**: 792–5.
42. Verschraegen CF, Levy T, Kudelka AP, *et al.* Phase II study of irinotecan in prior chemotherapy-treated squamous cell carcinoma of the cervix. *J Clin Oncol* 1997; **15**: 625–31.
43. Takeuchi S, Noda K, Yakushiji M, *et al.* Late phase II study of CPT-11, a topoisomerase I inhibitor, in advanced cervical carcinoma. *Proc Am Soc Clin Oncol* 1992; **11**: 224 (abstr 708).
44. Irvin WP, Price FV, Bailey H, *et al.* A phase II study of irinotecan (CPT-11) in patients with advanced squamous cell carcinoma of the cervix. *Cancer* 1998; **82**: 328–33.
45. Sugiyama T, Noda K, Yakushiji M. Multicentric phase II trial of irinotecan (CPT-11) and cisplatin as first-line chemotherapy in recurrent or advanced cervical cancer: Japan CPT-11 study group trial. *Proc Am Soc Clin Oncol* 1998; **17**: 352a (abstr 1360).
46. Rebattu P, Fumoleau P, Roche H, *et al.* Phase II trial of CPT-11 in advanced cervical carcinoma. *Proc Am Soc Clin Oncol* 1995; **14**: A737 (abstr).
47. Kavanagh JJ, Verschraegen CF, Kudelka AP. Irinotecan in cervical cancer. *Oncology* 1998; **12**: 94–98 (suppl 6).