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Perspectives and Commentaries

Progress in Chemotherapy of non-Small Cell Lung Cancer

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THE SURVIVAL of patients with non-small cell lung cancer remains unsatisfactory. In a recent series 5-yr survival was estimated to be 4%. Surgery and radiotherapy have probably achieved the best of their present possibilities and therapeutic advances are essentially expected from chemotherapy.

Hoffman and colleagues, in a recent review of chemotherapy of non-small cell lung cancer, observed that the combinations used before cisplatin and including cyclophosphamide, adriamycin, CCNU, methotrexate, procarbazine and vincristine led to a 20% objective response rate with few complete responses and a median survival time for responders ranging from about 30 to 60 weeks. As suggested by Cormier, using the MACC regimen (methotrexate, adriamycin, cyclophosphamide and CCNU), these regimens are probably superior to a placebo if survival is considered. However, polychemotherapy has not been demonstrated to be superior to single-agent therapy or single-agent sequential chemotherapy.

In this review we will focus on recent results obtained with combinations including cisplatin and/or new active drugs and thus explore the 'cisplatin era' in the chemotherapy of non-small cell lung cancer. Data have been collected from papers published in English oncology literature and/or presented at three recent important meetings: the 3rd World Conference on Lung Cancer (Tokyo, 1982), the 19th meeting of the American Society of Clinical Oncology (San Diego, 1983) and the 13th International Congress of Chemotherapy (Vienna, 1983).

Only series including more than 25 patients have been considered for evaluation response and survival. Although some prognostic factors have been identified in non-small cell lung cancer (performance status, loss of body weight, extension of disease and, possibly, prior therapy or histology), interrelations between them are not well known and in the majority of the papers reviewed here their role in response and survival was not studied.

NEW SINGLE DRUGS ACTIVE IN NON-SMALL CELL LUNG CANCER

Cisplatin, etoposide and vindesine, as indicated in Table 1, are presently the three most frequently investigated drugs. An evaluation of different series, including cases with and without prior chemotherapy, indicates an objective response rate of 14% (48/354), 9% (26/278) and 20% (57/287) respectively. These response rates are low. Other new or rediscovered agents are vinblastine, methyl-GAG, dianhydrogalactitol and ifosfamide. They have been investigated in limited phase II studies and, therefore, the reported response rates must be considered with caution. In a recent review Joss suggested that the new analogues of cisplatin, as well as mitoxantrone and bisantrene, might represent promising agents deserving further evaluation.

PHASE II STUDIES OF POLYCHEMOTHERAPY INCLUDING CISPLATIN AND OTHER ACTIVE DRUGS

Table 2 shows results obtained with regimens combining cisplatin with other cytostatic agents. The response rates range from 16 to 65% and the survival of responders from 24 to 79 weeks. Complete responses appear to occur more often

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Table 1. Monotherapy in non-small cell lung cancer

	No. of patients	Objective response (CR+PR) rate (%)
Cisplatin	354	48 (14)
Etoposide	278	26 (9)
Vindesine	287	57 (20)
Vinblastine	22	6 (27)
Methyl-GAG	42	3 (7)
Dianhydrogalactitol	63	6 (10)
Ifosfamide	75	30 (40)

with regimens combining cisplatin with vincristine or bleomycin. The median survival of responders exceeds 1 yr in patients receiving vincristine. In addition, a high dose of cisplatin (120 mg/m^2) appears also to be associated with a more prolonged survival while it does not exceed 1 yr for lower doses of cisplatin combined with adriamycin and cyclophosphamide or other drugs.

Table 3 indicates the results of phase II studies with cisplatin combined with etoposide and/or vincristine. An important observation here is the modest, although significant, number of complete responders in most of these series: it represents 4.5% of the evaluable patients (34/762). Moreover, in all these series, with the exception of Eagan's, who used a small dose of cisplatin (50 mg/m^2) in combination with etoposide, cyclophosphamide and adriamycin, the survival of responders was at least 1 yr.

In our analysis cisplatin and etoposide result in a response rate ranging from 18 to 38%. Natale, with a combination of high-dose cisplatin (110 mg/m^2), etoposide and methyl-GAG, obtained a 58% rate of response with 10% complete responses; however, these favorable results were not verified by Greenwald, who combined a lower dose of cisplatin (75 mg/m^2) with vindesine and methyl-GAG.

The cisplatin–vindesine regimens give a 30–40% response rate and the addition of bleomycin does not seem to improve the result. Regimens combining cisplatin, at 60 or 100 mg/m^2, with both etoposide and vindesine fail to induce a higher response rate than cisplatin and etoposide or cisplatin and vindesine. On the other hand, these regimens lead to a greater toxicity, consisting mainly of polyneuropathy, not reported with cisplatin and etoposide without vindesine.

Table 4 shows studies with miscellaneous combinations of potentially active drugs with or without cisplatin. Cisplatin, adriamycin and dianhydrogalactitol appear to induce a relatively high response rate. Vinblastine also appears promising in combination with cisplatin: in three reports, the response rate ranged from 15 to 55%; however, only one complete response has been reported and Woodcock observed four toxic deaths in 27 patients with vinblastine combined to a high dose of cisplatin (120 mg/m^2).

Renewed interest has been focussed on mitomycin C, which seems to induce a relatively high response rate and some complete responses in combination with vindesine or other drugs. Interestingly, a report comparing cisplatin and etoposide to mitomycin and adriamycin did not show differences in response rates, suggesting promising activity for mitomycin. These data are

Table 2. Results of combinations of cisplatin with 'older' cytostatic agents

Authors	Combination	Dose of cisplatin per course (mg/m$_2$)	No. of evaluable patients	Objective response rate (%)	No. of CR	Median survival time (weeks) Overall	Responders	NC	No response
Eagan	CDDP-ADR-CPA	40	69	38	–	–	–	–	–
Georgoulias	CDDP-ADR-VCR-BLM	100	46	42	4	30	–	–	–
Pearlman	CDDP-CPA-ADR-CCNU-VCR	50	17	47	6	–	–	–	–
Takita	CDDP-ADR-5FU-MTX-VCR	45	35	37	3	53	62	–	32
Erichson	CDDP-ADR-CPA-VCR	120	37	51	6	–	–	–	–
Israel	CDDP-BLM	100	58	65	10	39+	–	–	–
Bjornsson	CDDP-ADR-CPA-VCR	50	64	22	–	20	53	34	19
Takita	CDDP-CPA-ADR-CCNU-VCR	50	35	65	4	47	79	–	16
Reddy	CDDP-ADR-CPA-5FU-MTX-VCR	45	37	19	–	–	58	54	21
Gralla	CDDP-ADR-CPA	120	46	28	–	26	68	–	17
Eagan	CDDP-ADR-CPA	60	42	48	–	25	49	–	18
Evans	CDDP-ADR-CPA	40	131	27	2	15	33	29	10
Kraus	CDDP-hexamethylmelamine	50	51	16	–	–	36	–	6
Vogl	CDDP-ADR-MTX-BLM	50	26	46	–	–	24	–	17
Knost	CDDP-ADR-CPA	40	54	35	–	38	54	–	21
Issel	CDDP-ADR-Ftorafur	60	45	24	3	25	–	–	15

CR: complete response; NC: no change.
CDDP: cisplatin; ADR: adriamycin; CPA: cyclophosphamide; VCR: vincristine; BLM: bleomycin; MTX: methotrexate; 5FU: 5-fluorouracil.

important for the development of new active combinations not including cisplatin; however, etoposide with cyclophosphamide was not found to be active.

RANDOMIZED STUDIES WITH REGIMENS INCLUDING CISPLATIN

Randomized studies, as indicated in Table 5, have explored different ways to use cisplatin. In each series complete responses have been reported in the patients receiving cisplatin and overall response rates were in the same range as those obtained in phase II studies (Table 4). Combinations including cisplatin were demonstrated to be significantly more effective, as far as objective response is concerned, than adriamycin, cyclophosphamide, vincristine and CCNU, or adriamycin and cyclophosphamide or adriamycin, cyclophosphamide and vincristine.

Cisplatin plus etoposide was also shown better than etoposide, cyclophosphamide and adriamycin without cisplatin and randomized studies comparing vindesine and cisplatin to vindesine alone or vindesine and cyclophosphamide have also confirmed the superiority of the combination of cisplatin and vindesine.

Thus chemotherapy including cisplatin induces more responses than other regimens, such as with cyclophosphamide and adriamycin, single drug therapy with vindesine or combinations of vindesine or etoposide with drugs other than cisplatin.

Some reports compared schedules at different dosages of cisplatin with vindesine or etoposide, showing some advantage of high-dose cisplatin (120 mg/m^2) in increasing survival time and response rate. However, in a randomized study using cisplatin, adriamycin and cyclophos-

Table 3. Combination studies including cisplatin and etoposide and/or vindesine

Authors	Combinations	Dose of cisplatin per course (mg/m$_2$)	No. of evaluable patients	Objective response rate (%)	CR	Median survival time (weeks) Overall	Responders	NC	No response
Longeval	CDDP-VP16	60	94	38	4	30	60	-	23
Eagan	CDDP-VP16-ADR-CPA	50	28	46	-	30	38	-	16
Natale	CDDP-VP16-MGBG	110	53	58	5	-	53+	-	26
Klastersky	CDDP-VP16-VDS	60	62	40	5	-	53	-	30
Itri	CDDP-VDS-BLM	120	52	35	3	-	69	-	-
Gregor	CDDP-VDS	100	55	31	3	38	64	-	26
Greenwald	CDDP-VDS-MGBG	75	32	38	3	-	-	-	-
Niederle	CDDP-VDS	100	30	40	-	-	-	-	-
Porter	CDDP-VP16-VDS	60	72	25	3	-	-	-	-
Gropp	CDDP-VP16-VDS	100	77	16	1	-	-	-	-
Gatzemeier	CDDP-VP16-VDS	100	60	40	3	-	-	-	-
Giaccone	CDDP-VP16	60	28	18	1	-	-	-	-
Rinaldi	CDDP-VP16	100	51	37	-	31	-	-	-
Scagliotti	CDDP-VP16	100	30	27	2	-	-	-	-
Veronesi	CDDP-VP16	100	38	29	1	-	-	-	-

CR: complete response; NC: no change.
CDDP: cisplatin; ADR: adriamycin; CPA: cyclophosphamide; MGBG: methyl-GAG; BLM: bleomycin.

Table 4. Combination studies with other active drugs with or without cisplatin

Authors	Combination	Dose of cisplatin per course (mg/m$_2$)	No. of evaluable patients	Objective response rate (%)	No. of CR	Median survival time (weeks) Overall	Responders	NC	No response
Eagan	CDDP-ADR-DAG	60	37	67	-	38	54	-	24
Halibey	CDDP-VBL	100	27	15	-	-	-	-	-
Woodcock	CDDP-VBL	120	27	52	-	22	-	-	-
Miller	MMC-VDS-5FU	-	63	21	-	13	-	-	-
Livingston	MMC-BLM-ADR-CPA	-	45	11	2	23	44	-	-
Rosi	MMC-ADR-5FU	-	30	33	1	25	43+	-	22
Luedke	MMC-VDS	-	59	36	1	-	-	-	-
Morasco	VP16-CPA	-	27	7	-	-	-	-	-
Niell	CDDP-VBL-MTX-MMC	40	38	55	1	-	39	-	28

CR: complete response; NC: no change.
ADR: adriamycin; CDDP: cisplatin; VBL: vinblastine; MTX: methotrexate; MMC: mitomycin C; BLM: bleomycin; CPA: cyclophosphamide; 5FU: 5-fluorouracil; DAG: dianhydrogalactitol; VDS: vindesine; VP16: etoposide.

phamide with two dosages (50 mg/m² and 100 mg/m²) of cisplatin, Davis did not report improved results with the high dosage of cisplatin.

A few trials were designed to compare cisplatin and vindesine with cisplatin and etoposide to cisplatin, etoposide and vindesine or cisplatin and vinblastine. No statistically significant differences in response are apparent so far; in addition, the use of different doses of cisplatin in these regimens sometimes complicates the interpretation.

Finally, the addition of adriamycin to cisplatin, vindesine and cyclophosphamide and the addition of cyclophosphamide or ifosfamide to cisplatin and adriamycin were not associated with improved results.

It is difficult, at the present time, to obtain conclusions as far as survival data are concerned; they are missing in most series. Furthermore, ali the studies reviewed have less than 50 patients in each series. As the response rate is rarely greater than 50%, It is not surprising that statistical differences could not be observed as far as median survival is concerned.

COMPLETE RESPONDERS IN NON-SMALL CELL LUNG CANCER

Complete responders to chemotherapy are now being reported for non-small cell lung cancer. In four consecutive studies using cisplatin and vindesine Gralla obtained 23 complete responses in 271 treated patients (8.5%); it should be noted that complete responses were not restricted to

Table 5. Randomized studies comparing cisplatin-containing combinations to regimens with or without cisplatin

Authors	Combination	Dose of cisplatin per course (mg/m_2)	No. of evaluable patients	Objective response rate (%)	Median survival time (weeks)				
					CR	Overall	Responders	NC	No response
Joss	ADR-MMC	-	22	18	1	-	-	-	-
	CDDP-VP16	80	25	28	1	-	-	-	-
Block	CDDP-ADR-CPA-CCNU-VCR	50	28	29	2	32	-	-	-
	ADR-CDA-CCNU-VCR	-	20	5 (S)	-	26 (NS)	-	-	-
Paccagnella	CDDP-VDS	100	25	56	3	-	-	-	-
	CDDP-VP16	100	26	36	1	NS	-	-	-
	ADR-CPA	-	25	4 (S)	0	-	-	-	-
Statopoulos	CDDP-VDS	120	15	53	-	-	51+	26	-
	ADR-CPA-VCR	-	15	20	-	-	64	26	-
Elliott	VDS	-	18	6	-	-	-	-	-
	CDDP-VDS	100	15	53 (S)	-	-	-	-	-
Briancon	CDDP-VDS	120	19	68	2	32	60	26	-
	CPA-VDS	-	23	30 (S)	0	32 (NS)	43	26	-
Sculier	CDDP (60 mg/m²)-VP16	60	42	21	2	-	-	-	-
	CDDP (120 mg/m²)-VP16	120	43	35	1	-	-	-	-
Davis	CDDP-ADR-CPA	50	23	4	-	15	-	-	-
	CDDP-ADR-CPA	100	27	7 (NS)	-	21	-	-	-
Dhingra	CDDP-VDS	120	34	24	-	-	-	-	-
	CDDP-VP16	80	32	19	-	-	-	-	-
	CDDP-VDS-VP16	60	32	19 (NS)	-	-	-	-	-
Hosti	CDDP-VDS	90	23	83	3	-	-	-	-
	CDDP-V16	90	25	52	2	-	-	-	-
Kalman	CDDP-VDS	120	-	33	-	-	-	-	-
	CDDP-VBL	120	99	40 (NS)	-	-	-	-	-
Kelsen	CDDP-VDS-ADR-CPA	120	35	24	2	39	77	34	17
	CDDP-VDS-CPA	120	33	36 (NS)	2	39 (NS)	-	-	-
Araujo	CDDP-ADR-CPA	60	40	35	2	21	34	21	-
	CDDP-ADR-Ifosfamide	60	40	33 (NS)	3	21 (NS)	-	-	-
Fuks	VP16-CPA-ADR	-	29	10	1	23	-	-	-
	CDDP-VP16-CPA-ADR	40	36	28 (S)	4	35 (S)	-	-	-
Gralla	CDDP (60 mg/m²)-VDS	60	41	46	3	-	43	-	2
	CDDP (120 mg/m²)-VDS	120	40	40	5	-	93 (S)	-	-

CR: complete response; NC: no change.
S: statistically significant difference; NS: not statistically significant.
CPA: cyclophosphamide; ADR: adriamycin; CDDP: cisplatin; VDS: vindesine; VBL: vinblastine; MMC: mitomycin C; VP16: etoposide.

patients with good performance status and limited disease. The median duration of response was 18 months (range 10–48+ months) and the median survival was 29 months; all of these patients had an improved quality of life. The central nervous system was a common site of relapse (40%). Klastersky treated 149 patients in two different protocols, with cisplatin and etoposide, and obtained nine complete responses (6%); four of these patients had initially extensive disease. The median duration of response was 16 months (range 9–30 months) and the median survival was 18(+) months (range 15–39+ months). So far, two patients (22%) have relapsed in the brain and five in the chest.

CONCLUSIONS AND PERSPECTIVES

Chemotherapy with a combination of cisplatin and vindesine or cisplatin and etoposide appears to be more effective than that using other agents such as adriamycin, cyclophosphamide or nitrosoureas. Vinblastine, vincristine, bleomycin, methyl-GAG and dianhydrogalactitol might also be active, when combined with cisplatin. Cisplatin-containing combinations led, in most series, to a 30–40% overall response rate, with 5% complete responses. High doses of cisplatin might be associated with improved results as compared to a lower dosage. Although cisplatin-containing regimens probably represent an important advance in the treatment of non-small cell lung cancer, much work remains to be done. New drugs are needed, as well as better understanding of their use. Further progress might be made with new combinations of known drugs, alternating non-cross-resistant combinations and, perhaps, high doses of etoposide in combination with optimal dosage of cisplatin. Mitomycin C also appears to be a promising drug to be included into new combinations.

Efforts should be made to increase the complete response rates. Probably only with regimens capable of resulting in a high response rate, as is the case for small cell lung cancer, should one be able to improve the survival. It is also important to define more precisely the role of various prognosis factors such as performance status, extension of disease, loss of body weight, histological type of the tumor and prior therapy. Only the evaluation of larger series than those presently available will make it possible to clarify these important questions.

SUMMARY

We reviewed the results in the literature on chemotherapy with cisplatin and/or other new agents such as etoposide and vindesine in the treatment of non-small cell lung cancer. Associations of cisplatin with vindesine or etoposide have been overall superior to combinations of older cytostatic agents. These combinations result in an average of 30–40% objective response rate with 5% complete responses. High doses of cisplatin seem to be associated with optimal results.

Vinblastine, vincristine, bleomycin, methyl-GAG and dihydrogalactitol appear to be promising in combination with cisplatin.

(Bibliography is available from the above address.)