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Non-small-cell lung cancer: which platinum for gemcitabine?

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Cisplatin-based chemotherapy remains the backbone in the treatment of non-small-cell lung cancer (NSCLC), with significantly improved survival and better quality of life [1]. Platinum based doublets, with new drugs like Gemcitabine, Vinorelbine and Taxanes, are superior to single agent chemotherapy and should be preferred in first line treatment of patients with advanced NSCLC, according to current American Society of Clinical Oncology (ASCO) guidelines [2].

Gemcitabine (2,2-difluorodeoxicytidine) has shown good clinical activity against NSCLC, with synergism with cisplatin in preclinical studies [3]; the combination cisplatin-gemcitabine is today one of the reference treatments in NSCLC, showing superiority when compared with cisplatin doublets and triplets using other drugs like etoposide, mitomycin, vindesine and ifosfamide.

Several phase II and phase III trials with these combinations achieved response rates of 28–54 %, with improvement in time to progression and survival [4–10].

Relevant toxicity, namely myelosuppression with trombocytopenia, emesis, neurotoxicity, nephrotoxicity and the need for hydration are the main limits associated with the use of cisplatin; because of these side effects many medical oncologists remain sceptical about the utilization of this drug to treat patients with advanced NSCLC [11].

Carboplatin, an analogous of cisplatin, shows similar mechanism of action, but has different pharmacokinetics and toxicities, that make of it, in some way, a different drug [12]. In particular, a less non hematological toxicity and an increased convenience in an outpatient setting are balanced by a higher myelosuppression, particularly thrombocytopenia, which limits its combination with other drugs at a full dose. Because of a good activity with an easier administration and a milder non hematological toxicity, Carboplatin has often replaced Cisplatin in few malignancies, such as ovarian and breast cancer [13–16].

In NSCLC, several phase II studies have evaluated the combination of Gemcitabine-Carboplatin, using 3 weeks as well as 4 weeks schedule [17–23], with encouraging results in terms of response rate and survival.

Only one study compared 21-day and 28-day schedules; response rate and survival were similar, with a significant reduction of thrombocytopenia in the patients receiving the 21-day schedule [19].

Oxaliplatin is the newer platinum compound entered in clinical practice; in a phase II study in patients with NSCLC it showed activity as single agent, with an overall response rate of 16%.

Given its synergy with Gemcitabine, the combination Gem-Ox was evaluated in few phase II studies, achieving a response rate in the range of 16–43% [24–26].

Toxicity, hematological and non hematological, was mild, also in elderly and pretreated patients.

Although Cisplatin-based chemotherapy is currently considered to be the standard treatment in advanced NSCLC, many attempts to circumvent Cisplatin induced toxicity, replacing it with Carboplatin, have been made.

Go et al. [27], reviewed the comparative pharmacology and clinical activity of Cisplatin and Carboplatin in several tumors. Prospective randomized trials were identified for ovarian ($n = 12$), germ cell ($n = 4$), NSCLC ($n = 1$), SCLC ($n = 3$) and Head and Neck ($n = 4$) cancers. In those trials Carboplatin was found to be inferior to Cisplatin in germ cell, head and neck and esophageal cancer; conclusions were that Carboplatin does not possess equivalent activity to Cisplatin in all platinum-sensitive tumors. On the other hand, comparisons between Cisplatin and Carboplatin in NSCLC have been based on limited data.

Recently a meta-analysis of randomized clinical trial comparing Cisplatin to Carboplatin in patients with advanced NSCLC has been published [28].

Eight phase III trials (2948 patients) were identified in which doublets with Carboplatin were compared to doublets with Cisplatin; five of these trials investigated drug regimens containing a platinum plus a new agent (two studies with Gemcitabine, two with Paclitaxel and one with Docetaxel).

The response rate to Cisplatin-based chemotherapy was superior to that of Carboplatin-based chemotherapy in all eight single trials.

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The difference was highly significant considering all the eight trials (OR 1.36; 95% CI 1.15–1.61; $P < 0.001$) and also the five trials with Platinum plus a new agent (OR 1.38; 95% CI 1.14–1.67; $P = 0.001$).

Considering all eight trials, Cisplatin-based chemotherapy was associated with only a 5% improvement in Overall Survival, as compared with Carboplatin-based chemotherapy, and the difference was not statistically significant.

On the contrary, subset analysis of the five trials revealed that Cisplatin plus a new agent yielded an 11% significant superior survival as compared to Carboplatin (HR 1.11; 95% CI 1.00–1.22; $P = 0.039$) (Tables 1 & 2).

Patients treated with Cisplatin-based regimens more frequently developed nausea and vomiting, whereas thrombocytopenia was significantly more frequent in Carboplatin-based chemotherapy.

No significant difference in treatment related mortality was observed between Cisplatin and Carboplatin regimens.

The two studies in which the platinum compound was associated with Gemcitabine were relatively small with 120 and 176 patients respectively [29, 30]; for this reason no definitive conclusion can be drawn from these single studies.

In detail, Mazzanti et al. treated, in a randomized phase II trial, 62 patients with advanced NSCLC with GP (Gemcitabine 1200 mg/m^2, days 1 and 8, plus Cisplatin, 80 mg/m^2, day 2, every 21 days) and 58 with GC (the same Gemcitabine regimen plus Carboplatin at AUC 5 on day 2, every 21 days).

The objective response rate was 42% for GP, and 31% for GC ($P = 0.29$); median survival and median time to progression were 10.4 months and 6.7 months for GP and 10.8 months and 5.1 months for GC ($P = 0.39$ and $P = 0.77$, respectively).

Both regimens were well tolerated, with no statistical difference between arms in grade 3/4 toxicities.

The other trial with a platinum compound plus Gemcitabine is a randomized phase III trial, in wich 87 patients were treated with GP (Gemcitabine 1200 mg/m^2, on days 1 and 8 plus Cisplatin 80 mg/m^2 on day 1 every 21 days), and 89 patients were treated with GC (Gemcitabine as above, plus Carboplatin at AUC 5 on day 2, every 21 days).

Tolerability was the primary end point: patients with at least one grade 3/4 toxicity, excluding nausea, vomiting and alopecia, were 44% in GP arm and 54% in GC arm ($P = 0.17$).

The only statistically significant difference in toxicity was nausea and vomiting worse for Cisplatin arm (18% vs. 6%; $P = 0.01$) and thrombocytopenia, worse for Carboplatin arm (16% vs. 33%; $P = 0.01$).

The overall response rate, the median time to progression and the median survival were 41–29%, 5.9–4.7 months and 8.7–8.0 months for GP and GC, respectively; no difference was statistically significant, but, as shown also in the study of Mazzanti, all results were better with Cisplatin.

In conclusion, the data derived mainly from the meta-analysis of Hotta et al. show that, in patients with advanced NSCLC, combination chemotherapy of Cisplatin plus a new agent provide a significant survival improvement, as compared with Carboplatin plus the same new agent, with higher incidence of nausea and vomiting, and lesser thrombocytopenia, and for these reasons Cisplatin should be again considered the first choice for the combination Chemotherapy with a new drug in NSCLC.

On the other hand, the combination of Carboplatin plus a new drug, and particularly with Gemcitabine, can be an acceptable option for patients with NSCLC, which for any reason can be unable to receive a Cisplatin-based regimen.

Table 1. Responses in five trials comparing cisplatin-based with carboplatin-based chemotherapy

Authors	Chemotherapy	Patients	OR (%)	Odd Ratio	95% CI
Rosell 2002	P+T	284	28	1.17	0.81 to 3.97
	C+T	279	25		
Schiller 2002	P+T	288	21	1.29	0.85 to 1.97
	C+T	290	17		
Zatloukal 2003	P+G	87	41	1.71	0.92 to 3.20
	C+G	89	29		
Fossella 2003	P+D	408	32	1.47	1.08 to 2.01
	C+D	406	24		
Mazzanti 2003	P+G	62	42	1.60	0.76 to 3.40
	C+G	58	31		

Table 2. Survival in five trials comparing cisplatin-based with carboplatin-based chemotherapy

Authors	Chemotherapy	1-Year survival (%)	OS (months)	*P*	HR	95% CI
Rosell 2002	P+T	38	9.8	.02	1.21	1.05 to 1.40
	C+T	33	8.2			
Schiller 2002	P+T	31	7.8	NS	0.96	0.83 to 1.10
	C+T	34	8.1			
Zatloukal 2003	P+G	33	8.8	.90	1.01	0.77 to 1.32
	C+G	36	8.0			
Fossella 2003	P+D	46	11.3	NA	1.19	1.05 to 1.36
	C+D	38	9.4			
Mazzanti 2003	P+G	42	10.4	0.39	1.12	0.95 to 1.32
	C+G	43	10.8			

disclosures

Dr Boni has indicated that he has acted as a consultant for Eli Lilly.

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