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Editorial Comment

Chemotherapy for advanced lung cancer

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The natural history of untreated, advanced non-small cell lung cancer (NSCLC) is a median survival of four to five months, and a one-year survival (1YS) rate of less than 10%. Chemotherapy can prolong life expectancy and improve symptoms compared with best supportive care (BSC) without impairing quality of life (QOL) [1]. The platinum analogues, cisplatin and carboplatin, in combination with a third generation cytotoxic (gemcitabine, vinorelbine or a taxane) have similar efficacy, but differ in their side-effect profile. Response rates of 30–40% can be expected with median survival (MS) and 1YS of eight to 10 months and 30–40%, respectively. Second-line chemotherapy with docetaxel [2] or pemetrexed [3], and now third-line therapy with the epidermal growth factor receptor inhibitor, erlotinib (Tarceva) [4], can also provide modest improvements in survival and palliate symptoms compared with BSC. Whereas treatment options for these patients were once very limited, many can now expect to survive one year and even reach the two year milestone.

The clinical benefit of platinum combination chemotherapy is evident for patients with a performance status (PS) of 0 or 1. Usually a regimen is given for a maximum of six cycles, but equivalent efficacy has been demonstrated for three cycles [5], and the median number given in large randomised trials is frequently less than six cycles. For PS 2 patients, there is concern that the toxicity of the regimens used to treat PS 0–1 patients outweighs the benefit. Adverse events and inferior survival may actually be related more to the disease process than the regimens used [6]. However, single-agent chemotherapy (gemcitabine, vinorelbine, taxane), carboplatin-based or low-dose cisplatin-based combination regimens may represent alternative options for PS 2 patients and trials to evaluate these possibilities are underway [7]. For patients with PS of 0–1, there is a choice of platinum combinations for first-line treatment. Key questions that have been addressed by recent studies include:

1. Is there a 'best' platinum combination?
2. Can carboplatin replace cisplatin?
3. Is platinum necessary?

Is there a 'best' platinum combination?

The Eastern Cooperative Oncology Group (ECOG 1594) study in over 1000 patients of cisplatin–docetaxel, cisplatin–gemcitabine or carboplatin–paclitaxel compared with cisplatin–paclitaxel detected no significant differences in survival or response rates [8]. Similar efficacy parameters have also been demonstrated for vinorelbine–cisplatin compared with carboplatin–paclitaxel [9]. In the large, 1218 patient TAX 326 study, there was a non-significant trend to higher 1 and 2 year survival in patients who received cisplatin–docetaxel [10]. The 1 and 2 YS rates were 46% and 21% for the cisplatin–docetaxel arm, compared with 36% and 14%, respectively, for cisplatin–vinorelbine. Compared with ECOG 1594, there were more patients per treatment arm, a higher proportion of stage IIIB patients (33% *v* 13%), a lower proportion of patients with brain metastases (2% *v* 13%), and a higher median number (five versus four in ECOG 1594) of treatment cycles in the TAX 326 study. Recently a meta-analysis of 4556 patients from 13 randomised trials has demonstrated an absolute benefit in 1YS of 3.9% for gemcitabine–platinum compared with other platinum regimens [11]. These data suggest gemcitabine or docetaxel in combination with platinum to be among the most

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active regimens for advanced NSCLC at the present time, but there is not a clear winner (Table 1).

Can carboplatin replace cisplatin?

In a study of 618 patients randomised to receive paclitaxel–carboplatin, the MS was 8.2 months versus 9.8 months for paclitaxel–cisplatin (hazard ratio 1.22, 90% Confidence Interval (CI) 1.06–1.40; $P = 0.019$); the 1YS was 33% vs. 38%, and the 2YS rates were 9% vs. 15%, respectively [12]. Despite an increased incidence of vomiting with cisplatin, overall QOL (European Organisation for Research and Treatment of Cancer-Quality of Life-Core 30 questionaire (EORTC QLQ-C30) and LC-13) was similar. In the TAX 326 trial, docetaxel–cisplatin was also superior to docetaxel–carboplatin in terms of survival (Table 1), but not toxicity. In a meta-analysis of 2306 patients treated in randomised trials which used the same new agent (paclitaxel, docetaxel, gemcitabine) with only the platinum drug differing among the treatment arms, there was a modest survival benefit for platinum with a MS of 9.8 months (95% CI: 8.8–10.7 months) for cisplatin-based regimens and a MS of 8.7 months (95% CI: 7.9–9.9 months) for carboplatin [13]. Therefore, cisplatin may be marginally more active, but carboplatin is an acceptable alternative particularly where decreased toxicity is desirable or use of cisplatin is contraindicated.

Is platinum necessary?

A randomised study in 509 patients demonstrated MS times of 10.4 months (95% CI, 8.8 to 12 months) for paclitaxel–carboplatin and 9.8 months (95% CI, 8.0 to 11.7 months) ($P = 0.32$) for paclitaxel–gemcitabine combinations with 1YS rates of 41.7% and 41.4%, respectively. Neither toxicity nor cost of treatment differed significantly between the groups [14]. A recent meta-analysis of 37 clinical trials performed in 7633 patients has demonstrated a 60% increase in the Odds Ratio(OR) for response attributable to platinum-based therapy (OR 1.60, 95% CI 1.44–1.77, $P < 0.0001$), but no statistically significant increase in 1YS, when platinum therapies were compared with third-generation-based combinations (OR 1.11, 95% CI 0.96–1.27, $P = 0.15$). The platinum combinations caused more haematological toxicity, nephrotoxicity, nausea and vomiting, but no increase in neurotoxicity, febrile neutropenia rate or the toxic death rate [15]. These data suggest a role for non-platinum regimens in the first-line treatment of PS 0 or 1 patients. However, the EORTC recently reported on 480 patients treated with cisplatin–paclitaxel, cisplatin–gemcitabine,

Table 1
Selected Phase III trials of chemotheraphy for advanced NSCLC

Study	Regimen	N	MS	1YS %	2YS %	Toxicity	QOL
First-line							
Kelly	PV	202	8	36	16	↑ Neutropenia, vomiting	Equivalent
	CT		8	38	15	↑ Neuropathy	
E 1594	PT	1207	7.8	31	10	–	Not reported
	PG		8.1	36	13	↓ Haemoglobin, platelets	
	PD		7.4	31	11	–	
	CT		8.1	34	11	↓ Vomiting	
TAX 326	DP	1218	11.3	46	21	–	↓ Pain
	DC		9.4	38	18	–	–
	VP		10	41	14	↑ Anaemia, vomiting	–
Gridelli	GV	501	32 Wks	?	?	↓ Myelosuppression, vomiting, ototoxicity	–
	GP or VP		38 Wks			–	↓ Pain, cough
Kosmidis	CT	509	10.4	41.7	?	Equivalent	Not reported
	TG		9.8	41.4	?		
EORTC	PT	480	8.1	35.9	?	–	Equivalent
	PG		8.9	33.1	?	↓ Alopecia, neuropathy	
	TG		6.7	26.7	?	↓ Vomiting	
Georgoulias	GD	317	9.5	39	17		Not reported
	PG		10	42	17	↑ Neutropenia, nausea	
Second-line							
Hanna	D	571	7.9	29.7	?	↑ Febrile neutropenia	Equivalent
	Px		8.3	29.7	?		
Second or third-line							
Shepherd	Erlotinib	731	6.7[a]	31		Rash, diarrhoea	↓ Pain, cough, SOB
	Placebo		4.7	22			

Abbreviations. N, number of patients randomised; P, cisplatin; V, vinorelbine; C, carboplatin; T, paclitaxel; G, gemcitabine; D, docetaxel; MS, median survival in months; 1YS, 1 Year survival; 2YS, 2 Year survival; Pts, patients; Px, pemetrexed; QOL, quality of life; EORTC, European Organisation for Research and Treatment of Cancer; NSCLC, non-small cell lung cancer; wks, weeks.

[a] Overall survival; SOB, shortness of breath.

or paclitaxel–gemcitabine in a randomised trial that was well-balanced [16]. The MS for paclitaxel–gemcitabine was 6.7 months compared with 8.1 and 8.9 months for the other 2 arms. This difference was not statistically significant, but the trend to poorer survival for the non-platinum arm does cast doubt about its equivalence. In addition, the cost of the non-platinum arm was highest and the toxicity similar to the platinum arms. The EORTC will therefore continue to include a platinum combination as the reference arm in future trials.

Interestingly, docetaxel–gemcitabine compared with docetaxel–cisplatin was equivalent in survival outcome and less toxic in a phase III trial of 441 patients [17]. In light of the TAX 326 [10] and gemcitabine meta-analysis [11], further evaluation of this non-platinum regimen may now be warranted. A further possibility is docetaxel–irinotecan that has demonstrated promising activity, comparable to docetaxel–cisplatin, in a randomised phase II study [18]. One caveat is that non-platinum and platinum combinations with equivalent survival should not be assumed to provide similar symptom control. In the GEMVIN trial that compared gemcitabine–cisplatin or vinorelbine–cisplatin with gemcitabine–vinorelbine in 507 patients, QOL scores were equivalent in both arms. Acute toxicity due to vomiting, and decreased appetite, was significantly greater in the platinum-based arm. However, reduction of pain and cough was significantly better in the platinum-based arm [19].

The question now is whether a single combination regimen can be recommended for all PS 0–1 patients with advanced NSCLC. The evidence to date remains inconclusive. Better predictors of response to available drugs and regimens are required. For example, over-expression of excision repair cross-complementing 1 (ERCC1) has been associated with poor response and survival in cisplatin-treated patients [20]. Mutations in the EGFR gene may also predict for response to gefitinib [21]. At present, the recommended empirical treatment for advanced NSCLC is still a platinum in combination with a third generation cytotoxic, and gemcitabine or docetaxel appear to be the most active of these. Future trials will continue to include QOL analyses and assessment of symptoms to establish clinical benefit where survival differences may be marginal. Studies should also now be incorporated to develop predictive biomarkers that may eventually lead to selection of treatment based on molecular characteristics, in a manner analogous to the treatment of pneumonia using antimicrobials, and eliminate the need to identify a single, empirical regimen.

Conflict of interest

Prof. N. Thatcher receives research support and honoraria from Astra-Zeneca, Aventis, Eli Lilly, Roche, Bristol-Myers-Squibb.

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