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# Current Controversies in Cancer

# Are Platinum Compounds Mandatory in the Treatment of Metastatic Non-Small Cell Lung Cancer?

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### INTRODUCTION

THE MANAGEMENT of metastatic non-small cell lung cancer (NSCLC) remains a difficult task for patient and physician alike, despite several advances in its treatment during the past two decades. The use of multi-agent chemotherapy for treating metastatic NSCLC is now accepted practice in many countries and there is solid evidence that such treatment, when compared with best supportive care alone, improves survival [1], reduces symptoms [2, 3] and is cost-effective compared with other routine health interventions [4]. Earlier controversies about whether to treat at all have been replaced by controversy over which patients to treat, which drugs to use and how aggressively to treat. The topic of this 'Current Controversy in Cancer' concerns the necessity of including the platinum-based compounds, cisplatin and carboplatin, in the treatment of metastatic NSCLC. To my mind they are, to date, critical to what success we have seen in treating this disease.

### SINGLE AGENT ACTIVITY FOR THE PLATINUM COMPOUNDS

Both cisplatin and carboplatin have demonstrable single agent activity in NSCLC. Cisplatin has demonstrated approximately a 20% objective response rate [5] and is considered one of the more active agents in NSCLC. Despite early contradictory evidence [6, 7] there appears to be no dose–response effect for cisplatin once a threshold dose of approximately 60 mg/m$^2$ has been reached [8, 9]. Carboplatin has produced a lower response rate (< 10%) but was associated with the longest median and highest 1-year survival in a large Eastern Cooperative Oncology Group ECOG trial [10]. It has far fewer side-effects than cisplatin [11]. Early problems with emesis and nephrotoxicity with cisplatin were overcome with the availability of newer anti-emetics and the development of standardised hydration regimens [12, 13]. Carboplatin's unpredictable haematological toxicity, particularly thrombocytopenia, has largely been resolved by relatively simple dosing regimens based on creatinine clearance [14]. Although the trials have been underpowered to detect a small difference, there has been no demonstration of a major difference between the platinum compounds for treating metastatic NSCLC when they are combined with other agents [15, 16]. I know of no direct comparison of cisplatin and carboplatin as single agents.

### CHEMOTHERAPY OF METASTATIC NSCLC BEFORE PLATINUM

Prior to the introduction of cisplatin in the late 1970s, there was almost no effective chemotherapy for metastatic NSCLC. Despite early enthusiasm for cytoxan-CCNU [17], MACC [18] and CAMP [19], none of these regimens were particularly effective in randomised phase III trials [20, 21]. Meta-analyses of therapy for metastatic [1], locally advanced [22] and adjuvant treated [23] NSCLC demonstrated no enhancement of survival with earlier non-cisplatin-containing regimens. Indeed at least one of the earlier adjuvant trials suggested a detrimental impact on survival of a non-cisplatin-containing regimen [24].

### DIRECT COMPARATIVE TRIALS

There are actually only a handful of trials that compare an agent with cisplatin to that agent alone. Yamamoto and colleagues [25] looked at various dual combinations of cisplatin, vindesine, doxorubicin, cyclophosphamide and epirubicin, as well as single agent cisplatin and vindesine for metastatic NSCLC. In the relevant comparison, vindesine plus cisplatin (response rate 26.7%, median survival 33 w) was superior to vindesine alone (response rate 11.8%, median survival 27 w). Unfortunately multivariate analyses were not performed. Brocato and colleagues in Buenos Aires compared ifosfamide, epirubicin and cisplatin to ifosfamide/epirubicin [26]. Response rates and survival were not different but most of the

patients had IIIB disease and all the responders were irradiated. Again, no multivariate analysis was done. Rosso and colleagues studied 216 NSCLC patients (IIIB and IV) treated with either etoposide or etoposide plus cisplatin [27]. The response rate was higher for the combination (26% versus 7%) but median survival was not (7.9 m versus 5.9 m). No multivariate analysis was reported.

The only study to assess this question adequately was reported by Le Chevalier, who compared navelbine-cisplatin with vindesine-cisplatin and with navelbine alone [28]. Response rates (30% versus 14%), median survival (40 w versus 31 w) and 1 year survival (35% versus 30%) were superior for navelbine-cisplatin compared with navelbine alone and a multivariate analysis showed a statistically significant improvement in survival for the two-drug versus one-drug comparison.

## CONCLUSION

The single-agent response data, the impact of cisplatin in the meta-analyses and the clear benefit for navelbine plus cisplatin versus cisplatin alone in the Le Chevalier trial speak eloquently of the positive role of cisplatin in this disease. In the context of how this controversy was posed, there is no choice but to conclude that the addition of a platinum compound is 'mandatory' when compared with using the same drug(s) without platinum. The data could be infinitely stronger, but the compelling phase II data for each of the platinum-containing dual combinations compared with the earlier single agent results has left virtually every investigator uninterested in the 'x' plus platinum versus platinum alone comparison.

That its use to date has been 'mandatory' does not mean that it will remain so. The availability of several newer agents [29–33] and the demonstration of their superiority to older regimens [34, 35] has been promising, but we are now seeing reports of combinations of newer agents without platinum compounds [36, 37]. In addition, the current Cancer and Leukaemia Group (CALGB) trial comparing paclitaxel and carboplatin to single agent paclitaxel should also shed light on this issue. Depending on the outcome of these studies, I may be forced to change sides in this controversy several years from now.


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## INTRODUCTION

NON-SMALL cell lung cancer (NSCLC) includes a group of tumours which respond poorly to drugs. Nevertheless, cisplatin-based polychemotherapy is often used, especially for treating advanced disease. The results are discouraging with a median survival, in patients with metastatic disease, of approximately 6 months. On this basis, we believe that quality of life should always be considered a primary endpoint of clinical trials for this subset of patients. We also think that costs analysis of treatment for advanced NSCLC should be performed whenever possible.

A recent meta-analysis showed only a small advantage, 6 weeks in median survival, for chemotherapy versus best supportive care in advanced NSCLC [1]. Data were available from 11 trials on 1,190 patients. No data were available on the impact of the treatment on quality of life and costs analysis. In fact, all the studies included in the meta-analysis except two lack quality of life assessment and costs evaluation. Ganz and colleagues, in the trial comparing supportive care versus supportive care plus cisplatin and vinblastine chemotherapy, planned a quality of life analysis using the Functional Living Index-Cancer (FLIC) [2]. Unfortunately, the authors were unable to report the results on quality of life measured by the FLIC because of incomplete data collection and difficulty with self-administration. The National Cancer Institute of Canada performed an economic evaluation of the trial comparing best supportive care versus chemotherapy with cisplatin and vindesine or cisplatin, doxorubicin and cyclophosphamide [3]. The authors demonstrated that supportive care may be less cost-effective than chemotherapy because of a higher rate of hospitalisation.

Among the studies included in the meta-analysis, eight trials used cisplatin-based chemotherapy, seven of which combined cisplatin with vinca alkaloids or etoposide. Out of the remaining three trials, two used long-term alkylating agents and one used etoposide as a single agent, which are inadequate regimens of chemotherapy with very low activity. Whilst cisplatin-based trials showed a benefit of chemotherapy, the outcome of trials testing non-cisplatin-based chemotherapy suggests a detrimental effect of chemotherapy. Our point of view on this issue is that, based on these trials, no conclusion can be drawn on the role of non-cisplatin-based chemotherapy in the treatment of metastatic NSCLC.

It is important for the future to develop effective non-cisplatin-containing regimens because cisplatin toxicity still remains a problematic feature, not completely solved by the improvement of supportive care. Namely, renal toxicity and delayed emesis, although prevented by hydration and antiemetics, and neurotoxicity may be major causes of patients distress. Furthermore, cisplatin toxicity may be worse for elderly patients, who constitute approximately half the number of NSCLC lung patients.

Mitomycin C plus vindesine is one of the most active regimens. In phase II studies of advanced NSCLC, response

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