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PII: S0959-8049(98)00311-6

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CISPLATIN AS a single agent does not possess a striking activity in advanced non-small cell lung cancer (NSCLC). Response rates with single agent cisplatin do not usually reach 20% and are probably in the range of 10–15%. However, until a few years ago, there were not that many drugs with a major response rate of over 15%, which was established as a cut-off point to call a drug active or inactive. Among the other active drugs were the vinca alkaloids (with the possible exception of vincristine), mitomycin-C and certainly ifosfamide, which may actually have a slightly higher response rate. Other drugs, such as the epipodophyllotoxins probably have a lower level of activity.

Cisplatin has been for many years considered an important part of combination chemotherapy for NSCLC. The reason for it was partly rational and partly simply based on the empirical process of combining 'active' drugs in order to try and achieve a better result. Cisplatin was found to be synergistic with a number of other antineoplastic agents in preclinical models [1]. From experience in germ cell tumours and small cell lung cancer, it was clear that the combination of cisplatin/etoposide was definitely more efficacious than either drug alone. This synergism has been much harder to show in advanced NSCLC, where response rates with this combination most frequently range between 20 and 30%. Large randomised trials were needed to demonstrate that cisplatin adds to etoposide alone or other agents [2–5]. As Dr Ruckdeschel points out in his paper, cisplatin combination chemotherapy has been considered standard treatment for

advanced NSCLC for at least the last decade. However, whether cisplatin is an essential drug is an unsettled issue. Dr Gridelli listed in his Table 1 the randomised studies showing that cisplatin in a two- or three-drug combination is not better than a two- or three-drug combination not including cisplatin. Much emphasis has been given to the use of cisplatin in NSCLC based on two important publications; the first showing that cisplatin was an independent positive prognostic factor for response and survival in the experience of SWOG in over 2,500 patients [6]. The other evidence comes from the large meta-analysis of chemotherapy in NSCLC [7], in which cisplatin-based chemotherapy gave a benefit in terms of survival in all stages of the disease. Intriguing were the detrimental results observed in older studies which did not include cisplatin and were mainly based on prolonged administration of alkylating agents. It is, however, difficult to conclude from these two retrospective studies whether cisplatin really made a difference, but, of course, the evidence is compelling.

The question whether cisplatin is an essential agent in the chemotherapy of NSCLC is an important one mainly for two reasons:

(1) Chemotherapy is considered standard treatment in fit patients with advanced NSCLC, and has become standard treatment in earlier stages of the disease, as part of a multimodality therapy (stage III).
(2) Cisplatin use is burdened by side-effects that are not easy to handle.

Toxicity is an important issue, because chemotherapy cannot cure metastatic NSCLC, and its major objective is palliation. Toxicity directly impinges on quality of life in a negative way. Severe nausea and vomiting, caused by cisplatin, can now be handled and prevented much more efficiently than a few years ago, by the use of potent anti-emetic medication (5-HT3 receptor antagonists and steroids). However, more chronic side-effects are not easy to handle. Nephrotoxicity can be prevented in the vast majority of patients by adequate hydration, but this usually requires prolonged hospital stay. Some degree of nephrotoxicity is common after several cycles of cisplatin chemotherapy. Other chronic and cumulative side-effects, such as peripheral neuropathy and hearing loss, cannot be adequately prevented and are usually not completely reversible. These considerations are, of course, even more important in patients with early stage of disease, where cure can be achieved.

The substitution of carboplatin for cisplatin is obviously appealing, as carboplatin is essentially devoid of nephrotoxicity and neurotoxicity at the doses usually employed. Moreover, it is far less ototoxic than cisplatin. However, there are two issues that require attention:

1. Carboplatin has more myelotoxicity than cisplatin, and this may constitute a problem in combining it with other myelotoxic agents.
2. The activity of carboplatin may be inferior to that of cisplatin.

Thrombocytopenia and neutropenia may represent a serious and cumulative haematological toxicity in combining carboplatin with other myelotoxic drugs. Until recently, a carboplatin dose was calculated by square metre; it is, however, clear that dosing according to AUC is a more appropriate way of giving carboplatin [8]. Excessive toxicity may be avoided, and eventually also efficacy can be positively affected. The difference in activity between cisplatin and carboplatin is unlikely to make a large difference in advanced NSCLC, although it may in earlier stages of the disease. Cisplatin still remains the platinum agent of choice in the treatment of germ cell tumours.

In the last few years, a substantial change has been observed in the scenario of chemotherapy for NSCLC: at least 4–5 new active drugs have been introduced into the treatment of this and other tumour types [9]. These are vinorelbine, gemcitabine, irinotecan and the taxanes, paclitaxel and docetaxel. Response rates when given as single agents are in the range of 20% and there are strong indications that combinations of vinorelbine, paclitaxel and gemcitabine with cisplatin not only improve response rates, but also survival over standard cisplatin-based chemotherapy in some randomised trials [3, 10, 11].

The obvious question is whether these new drugs by themselves will be as good or better than a cisplatin-based chemotherapy. New combinations are actively being investigated and some are reported in Table 2 of Dr Gridelli's paper. Although response rates appear promising, and are in the same range of results obtained by platinum-containing regimens, superiority (or equality) will only be ascertained by the painstaking process of randomised trials in advanced NSCLC. In these studies additional end-points need to be taken into consideration, in case no major differences in survival and response rate would appear, i.e. safety, quality of life and cost-effectiveness. Given the number of possible combinations of the new agents and with older drugs, it would be very important to have an efficient and reliable way of predicting in preclinical models what are the combinations which most likely will lead to synergistic activity, keeping toxicity acceptable. Unfortunately, the preclinical models we have are so far not satisfactory to this end, and are not commonly employed to try and devise a strategy for combination chemotherapy.

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