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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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rates ranged from 33 to 59% [4–7]. Two randomised comparisons of mitomycin C plus vindesine versus the combination of cisplatin plus vindesine yielded contrasting results [8, 9]. In the smallest trial (58 patients), the authors reported a significant advantage in the response rate for the cisplatin combination, with no difference in median survival [8]. In a large randomised trial, Luedke and colleagues reported no difference in response rate and survival among 247 randomised patients [9]. In another randomised trial comparing mitomycin C + vindesine versus mitomycin C + ifosfamide versus cisplatin + etoposide, no significant differences were seen in response rate and survival among the three arms but, on the basis of reported toxicity, mitomycin C plus vindesine was felt to be the preferred regimen [10]. In a large phase II study, we used a combination of mitomycin C + etoposide + vindesine (MEV) reporting a 37% response rate, with a 4.7% complete response and low toxicity [11]. Subsequently, we performed a phase III trial on 204 metastatic NSCLC patients comparing MEV to cisplatin + mitomycin C + vindesine combination (MVP). We observed no differences in symptom relief, response rate, and survival among the two arms with a significantly lower toxicity for MEV [12]. Unfortunately, validated methods of quality of life measurement for NSCLC patients were not available when the trial was started. However, although lacking a specific quality of life analysis, the study showed a highly significant difference in frequency and degree of toxicity between the two arms. In summary, in all reported randomised trials mitomycin C + vindesine based regimes were less toxic compared with cisplatin-based regimens (Table 1).

In the last few years, new drugs such as vinorelbine, gemcitabine and taxanes (paclitaxel, docetaxel) have been shown to be active in advanced NSCLC with approximately a 20% response rate as single agents [13–16]. In two different randomised trials, single agent gemcitabine showed a similar response rate and survival with less toxicity compared with the cisplatin + etoposide combination [17, 18]. Gralla and colleagues performed a phase I–II study on mitomycin C plus vinorelbine reporting a 34% response rate [19]. In phase II studies, the combination of ifosfamide plus vinorelbine induced objective responses in 25–40% of advanced NSCLC patients with median survival ranging between 9 and 11 months [20–23]. The combination of docetaxel with vinorelbine, in two reported phase II studies, induced response rates of 40.5% and 27% [24, 25]. The Cancer and Leukaemia Group B tested a new combination of paclitaxel and ifosfamide observing 34% objective responses [26]. In Table 2, data from trials on polychemotherapy regimens including new drugs are summarised. In addition, it is also important to emphasise that some of the more recently developed drugs (namely vinorelbine and gemcitabine) usually induce few and well manageable toxic effects. This could be a crucial point for future trials evaluating the impact of chemotherapy on patients' quality of life.

Table 1. Randomised trials on mitomycin C + vindesine-based chemotherapy versus cisplatin-based regimens in advanced NSCLC

Authors [Ref.]	Drugs	*n* pts	% OR	MS (weeks)
Shinkai [8]	MMC + VDS		10	40.1
	versus	58		
	CDDP + VDS		42.9	40.5
Luedke [9]	VDS		< 1	14.8
	versus			
	MMC + VDS	435	27	20.4
	versus			
	CDDP + VDS		19	24.7
Gatzemeier [10]	MMC + VDS		22.7	23
	versus			
	MMC + IFO	192	30	27
	versus			
	CDDP + VP-16		25	25
Gridelli [11]	MMC + VDS + VP-16		21.4	29
	versus	204		
	MMC + VDS + CDDP		28.7	28

OR, objective response; MS, median survival; MMC, mitomycin C; VDS, vindesine; CDDP, cisplatin; IFO, ifosfamide; VP-16, etoposide.

Table 2. Phase II trials on non-cisplatin new drug regimens in advanced NSCLC

Author [Ref.]	Drugs	*n* pts	% OR	MS (months)
Morere [20]	IFO + VNR	20	40	10.5
Pawel [21]	IFO + VNR	40	25	NR
Sparrow [22]	IFO + VNR	32	32	9
Vallejo [23]	IFO + VNR	40	33	11
Gralla [19]	MMC + VNR	36	34	10
Trillet-Lenoire [25]	TXT + VNR	34	27	NR
Kourosusis [24]	TXT + VNR	37	40.5	5
Perry [26]	IFO + TAX	20	34	NR

OR, objective response; MS, median survival; IFO, ifosfamide; VNR, vinorelbine; MMC, mitomycin C; TXT, taxotere; TAX, taxol; NR, not reported.

Several institutions are developing treatment programmes for advanced NSCLC, not including cisplatin. The EORTC Lung Cancer Cooperative Group is studying a combination of gemcitabine and paclitaxel. Our Institution is coordinating a multicentre phase II trial on the combination of gemcitabine and vinorelbine. In the U.S.A., at the Memorial Sloan-Kettering Cancer Center, a trial on docetaxel plus vinorelbine is in progress. The University of Rochester and the Vanderbilt University are testing a combination of paclitaxel and vinorelbine.

In conclusion, on the basis of data available from clinical trials, the use of cisplatin in the treatment of metastatic NSCLC is not mandatory, in our opinion. As this point is, without any doubt, one of the most debated issues of modern clinical oncology, we feel that it is mandatory to plan and perform clinical trials comparing new active and well-tolerated non-cisplatin-based polychemotherapy regimens with cisplatin-based regimens. It is also mandatory that such trials are planned with quality of life and costs-analysis as primary end-points.

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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