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Perspectives and Commentaries

Is There Standard Chemotherapy for Non-small Cell Lung Cancer?

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FOR THE majority of patients with lung cancer — about four fifths — whose tumors show 'non-small cell' histology, surgery remains the treatment of choice. Unfortunately, the poor physiological status of many subjects and the presence of locally advanced disease or distant metastases means that most patients (80%) with 'non-small cell lung cancer' (NSCLC) are inoperable from the outset. Even among apparently successfully operated patients, the emergence of occult metastases and the frequency of local tumor recurrence limit postoperative long term (5-yr) survival rates to 20–30%. There is a manifest need, therefore, for an effective form of systemic treatment which, if it were available, could be expected not only to prolong the survival of patients with advanced, inoperable disease but also, in an adjuvant setting, to improve the prospects for cure among surgically treated patients. Controlled studies number very few but, as yet, there have been none that have convincingly demonstrated significant survival benefit from chemotherapy in NSCLC. This applies to both single agent and combination chemotherapy, both for adjuvant studies and for patients with inoperable disease.

By contrast, many NSCLC studies have demonstrated 'activity' among a variety of drugs or drug combinations when the success of therapy has been measured in terms of objective tumor responses. Most of these studies fail to provide important data concerning the influence of chemotherapy on the patient's symptoms and quality of life. A measurable tumor response does not necessarily imply symptomatic benefit, while treatment related toxicity might well negate any temporary improvement in tumor related symptoms. A survival advantage has often been demonstrated among patients responding to chemotherapy as compared to non-responders. However, the latter generally comprise a higher proportion of patients with extensive disease or relatively poor performance status. It has yet to be proven, therefore, that this survival benefit in 'responders' represents a genuine effect of chemotherapy which is independent of prognostic factors.

The different 'mix' of prognostic factors among patient populations in different studies makes comparisons of treatment results fraught with difficulty. Controlled trials comparing single agents with combined regimes or studies contrasting two or more drug combinations are especially few. It is hardly surprising, therefore, that there is little or no consensus of agreement as to either the role of chemotherapy in NSCLC or what constitutes the most effective form of chemotherapy. It is particularly salutory to note that the initial enthusiasm generated in the past for a variety of drug combinations, generally based on results in single institutions, has had to be moderated when the same regimens have been re-assessed in larger, more carefully designed studies by co-operative groups [1, 2]. This lack of reproducibility may in part reflect variations in the pretreatment characteristics of the patient populations. However, a recent review of single agent chemotherapy in NSCLC [3] has highlighted the low order of activity (<15% mean response rate) of 'conventional' agents (cyclophosphamide, adriamycin, methotrexate, CCNU) that have hitherto figured so prominently in combined treatment regimens.

Collected data [3, 4] have shown mean response rates of >15% for only four agents: ifosfamide (26%), cisplatin (20%), mitomycin C (20%) and vindesine (17%). Other agents as yet inadequately studied (triazinate, mitoxantrone, new cisplatin analogues) or well tried drugs (adriamycin, vinblastine, etoposide, procarbazine, hexamethylmelamine, dibromodulcitol) when used in alternative doses or schedules may yet show a similar order of single agent activity. Understandably, however, the focus of investigation has turned upon these newer, more active drugs. In particular, the combination of vindesine and cisplatin, the subject of a recent contribution to this journal [5] has attracted

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considerable attention. Favourable reports for this and other cisplatin-based combinations have tended to encourage a degree of optimism resulting from the notion that effective chemotherapy for NSCLC is now available. It has become pertinent to ask, therefore, whether vindesine–cisplatin, or indeed any other regime, can have reasonable claim to be used as 'standard' treatment, having a routine place in the management of NSCLC.

The therapeutic activity of vindesine–cisplatin (VDS/DDP) in NSCLC was first commented upon by Gralla *et al.* [6] in a series of 85 patients, none of whom had received prior chemotherapy while all but three subjects had distant metastases. Patients were randomly assigned to receive vindesine with either high dose (120 mg/m^2) or low dose (60 mg/m^2) cisplatin. The mean response rate of 43% did not differ significantly in the two treatment groups. However, the high dose cisplatin regimen was found to be significantly superior to the low dose regimen in terms of both median duration of response (12 months vs. 5.5 months) and median survival duration among 'responders' (21.3 months vs. 10 months). All responding patients apparently either improved in performance status or maintained their initial status and this was often associated with symptomatic benefit.

In general co-operative group trials have tended to confirm the 'activity' of VDS/DDP in terms of objective remission rates with, most significantly, a small proportion of patients in most series achieving a complete tumour response (CR) — a rare occurrence in earlier studies using 'conventional' agents. In the most recently published study [5], a 33% response rate (8% CRs) was recorded in 63 patients using a regime (cisplatin 100 mg/m^2) similar to that described by Gralla. In this study nearly half of the subjects (48%) had disease initially limited to the chest, all patients were of good performance status and, as in Gralla's study, none had received prior chemotherapy. Despite this favourable 'mix' of prognostic factors both the median response duration (4 months) and median survival duration for responders (14 months) were disappointingly short. Using a similar regime with an identical dose of cisplatin in a similar patient population, our own group experience of VDS/DDP [7] is in remarkably close agreement with these findings: 33% objective response rate in 43 evaluable patients; median response duration, 4 months; median survival duration of "responders", 13 months. In this randomized study, VDS/DDP proved to be superior to VDS as a single agent both in terms of response rate and survival. This survival advantage was relatively small, however, with overall median survival times of 9 months and 4 months for the two arms, respectively (unpublished data based on 2-yr survival figures). Furthermore, the survival benefit associated with VDS/DDP was not apparent among patients with extensive stage disease and was confined to patients with favourable prognostic factors.

In both U.K. studies treatment was often followed by a deterioration in performance status even among responding patients. Furthermore, subjective treatment toxicity was considerable and cumulative effects prevented continuation of chemotherapy beyond 20 weeks in either study. Neurotoxicity and myelotoxicity of either moderate or severe degree can be expected in 59% and 33% of patients, respectively [6].

Using vindesine and cisplatin as a basic regimen various attempts have been made to improve response rates by the use of additional 'active' agents. Comparable response rates, ranging between 30 and 40% have been achieved using VDS/DDP in combination with cyclophosophamide [8], cyclophosphamide plus adriamycin [8], bleomycin [9] and etoposide [10], with no clear advantage for any of these potentially more toxic regimens. A preliminary report suggesting an improved response rate, but without greater toxicity, using mitomycin C in combination with VDS/DDP needs confirmation (Kris MG *et al.* Abstract No. 225, ASCO 1984).

By definition "standard" chemotherapy for any tumour type should represent the best available. While VDS/DDP has certainly produced consistent results, there are few comparative data to suggest that any combined regimen is clearly superior to another or indeed that any drug combination is superior to any of the most active single agents. The study comparing VDS with VDS/DDP [7] is in fact one of only two existing randomized studies in NSCLC that have provided unequivocal evidence of superior response rates favouring drug combinations over single agents, the other study having compared dianhydrogalactitol with the combination of cyclophosphamide, adriamycin and cisplatin (CAP). Most of the available data relates to agents with minimal single agent activity and further controlled studies seem warranted comparing the more active drugs used singly and in combination.

While results comparable to those achieved with VDS/DDP have been claimed for CAP, this has not been a consistent finding [2]. Equally reproducible results have been obtained, however, with other cisplatin-based combinations. Vinblastine appears as effective as vindesine in combination with DDP (Kalman LA *et al.* Abstract No. 201, ASCO 1983). Longeval and Klastersky [11] reported a 38% response rate among 94 NSCLC patients using etoposide/DPP, and in a randomised comparison (Dhingra HM *et al.* Abstract No. 220, ASCO 1984) this combination was as

effective as VDS/DDP in terms of response rate, response duration and survival of responding patients. In an important ongoing study of metastatic NSCLC (Ruckdeschel JC *et al.* Abstract No. 171, ASCO 1984), VDS/DDP is the subject of a randomised comparison with etoposide/DDP, mitomycin C/vinblastine/DPP and CAMP (cyclophosphamide, adriamycin, methotrexate, procarbazine). Based on preliminary results in 551 patients no clear advantage has been demonstrated for any of these combinations in terms of either response rate or median survival. Furthermore, CAMP proved significantly less toxic than each of the cisplatin containing regimens.

CONCLUSIONS

The combination of cisplatin with either vindesine, vinblastine or etoposide can be expected to yield consistently reproducible objective tumour remission rates ranging between 30 and 40% in series of patients with inoperable NSCLC. Whereas tumour responses even of relatively brief duration might prolong survival in some patients, the magnitude of this survival benefit is unclear but is probably small and at least partially dependent upon prognostic factors. Treatment trials have placed insufficient emphasis upon the evaluation of patients' quality of life or the palliative as opposed to the toxic effects of chemotherapy. Improved performance status can be expected in patients achieving a complete remission, but this applies to only a small minority (5–10%) of patients receiving the cisplatin-based regimens cited above. The symptomatic benefit conferred by partial tumour responses is less clear-cut. Controlled studies are needed therefore to compare the quality vs. quantity of life in treated patients with controls receiving supportive treatment only. Until such a study provides more substantial evidence of therapeutic benefit none of the most 'active' drug combinations currently available can be regarded as having a standard place in the management of NSCLC. If VDS/DDP or any other cisplatin-based regime is accepted as standard treatment, investigative studies must of necessity be performed in previously treated patients in whom impaired responsiveness to 'second line' agents can be confidently predicted. On present evidence, it would seem unreasonable to allow any such chemotherapy standard to prejudice the search for still more active agents than those currently available. NSCLC should remain therefore an investigative proposition.

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