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Commentary

Chemotherapy in Non-small Cell Lung Cancer (NSCLC)

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(A COMMENT ON: Niitamo-Korhonen S, Holsti P, Holsti LR, Pyrhönen S, Mattson K. A comparison of *cis*-platinum–vindesine and *cis*-platinum–etoposide combined with radiotherapy for previously untreated localized inoperable non-small cell lung cancer. *Eur J Cancer Clin Oncol* 1989, **25**, 1039–1043.)

CHEMOTHERAPY (CT) for patients with NSCLC is often considered as a controversial issue on the basis of studies such as that presented by Woods *et al.* at the ASCO meeting in 1985; however, that study has never been published [1]. On the other hand, several other investigations indicate that CT in NSCLC patients is associated with a significant response rate and an improved survival of the treated patients [2, 3]. Prognostic factors are essential for the understanding of the results of CT in NSCLC. O'Connell *et al.* [4] have undertaken a prospective trial of 408 patients with NSCLC; they found that major prognostic factors for survival were (1) the performance status, (2) serum lactic dehydrogenase (LDH) level and (3) the presence of extrathoracic disease. If the significance of the LDH level is somewhat unclear, it is likely that the performance status and the absence of extensive disease (ED) are related. Thus, it appears important to separate, in studies of CT in NSCLC, those patients with so-called LD and ED. This has been only rarely done so far and, therefore, it is possible that many results of CT in NSCLC are biased by the regularly poor response in patients with extrathoracic disease. The need for stratified evaluation seems therefore important if the role of CT is to be objectively appreciated.

There are many compelling reasons why CT should be directed at patients with a minimal tumor burden. This is true whatever the nature of the tumor is and becomes especially valid when one is dealing with tumors that are not curable when treated at an advanced stage, which is the case for NSCLC.

There are several theoretical reasons why neo-adjuvant treatment, i.e. CT given prior to radiotherapeutical and/or surgical radical treatment, might be of particular benefit for NSCLC [5]; although most studies are still limited and preliminary, a few interesting aspects have emerged. It seems established that, after initial CT, surgery is feasible and safe, and that complete resection rates are high in groups of patients in whom, prior to CT, surgery was considered difficult or impossible. While the 'optimal' CT to be used in such circumstances has not been established yet, the study of patients with NSCLC, enrolled in neoadjuvant CT programs, provides a unique opportunity to evaluate chemotherapeutic regimens that are felt to be potentially active, in a special subgroup of patients with a limited tumor mass.

A review of the recent (1986–1988) reported trials of neo-adjuvant CT in NSCLC is summarized in Table 1. Most studies have been reported in an abstract form only, and the information to be derived from them is therefore often fragmentary.

Three types of CT have been investigated. The first category is cisplatin (CDDP) + vinca alkaloids or etoposide (VP16) [6–9]. CDDP + vindesine [10] or VP16 [11] are recognized as moderately active approaches to NSCLC, as well as CAP; it remains to be seen whether CDDP alone plays the major role in their activity or whether it is the combination which is important [12]. It is not surprising that such combinations have been selected for neo-adju-

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Table 1

No. studies [References]	No. patients	Response rates PR	CR	Median survival (months)	Overall conclusion* +/±/−
		Cisplatin + vindesine Cisplatin + vindesine + etoposide Cisplatin + vindesine + cyclophosphamide Cisplatin + Adriamcyin® + cyclophosphamide			
4 [6–9]	109	60 (55%)	1 (0.9%)	24–32	1/2/1
		Cisplatin + 5-FU Cisplatin + 5-FU + etoposide Cisplatin + 5-FU + vinblastine			
3 [14–16]	115	70 (61%)	1 (0.8%)	14–>18	1/2/0
		Cisplatin + vinblastine/vindesine + mitomycin			
7 [18–24]	218	121 (69%)	20 (11%)	14–19	4/2/1
		Total			
14	425	263 (62%)	22 (5.1%)	14–32	6/6/2

*Regarding the usefulness of proto-adjuvant chemotherapy prior to surgery ± radiotherapy: + = positive; ± = unclear; − = negative.

vant CT of NSCLC: in this issue of the Journal [13], Niitamo-Korhonen *et al.* report a comparative study of cisplatin-vindesine and cisplatin-etoposide as a proto-adjuvant approach prior to radiotherapy. The response rate, in these patients with limited tumors, was respectively 66% and 50%. The median survival, in both series, was in the range of 12 months.

The overall response rate, in other studies of neo-adjuvant therapy with these combinations (Table 1), appears to be also in the range of 55%, a figure similar to that reported by Longeval and Klastersky in NSCLC patients with LD treated with CDDP + VP16 [11]. On the other hand, the CR rate is low (1%).

Another combination reported for neo-adjuvant CT in NSCLC is CDDP + 5FU, with the possible addition of VP16 or vinblastine and radiotherapy [14–16]. Results are similar to those obtained with the preceding combination; the overall response rate is in the range of 61% with 0.8% CR; the median survival is 14–18 months.

For these two regimens, CDDP + vinca alkaloids and CDDP + 5FU, only two out of seven studies of neo-adjuvant CT claim unequivocal evidence of a benefit from CT in patients who subsequently underwent surgery.

The last and most often used regimen consists of CDDP + vinblastine/vindesine + mitomycin C [17]. That approach has been used for neo-adjuvant purposes in NSCLC in seven series so far [18–24] grouping 201 patients. The response rate was 66% with 10% CR and the overall median survival was 14–19 months. Four of seven studies claimed a definite advantage for the neo-adjuvant approach.

A few general conclusions can be proposed on the basis of the preceding review.

Firstly, it appears that CT of NSCLC, in patients with LD (who are potentially operable), is more active, in terms of response rate, than when applied to patients with more ED. As a matter of fact, under the latter circumstances, the response rate rarely exceeds 30% [25], while it is in the range of 60%, with the three regimens considered above and which were administered to NSCLC patients with LD, who were potential candidates for surgical resection. Whether these results can be improved further by manipulations of the presently available drugs remains to be studied. Our Group is presently studying the combination of CDDP + VP16 + 5FU + mitomycin C, in order to take optimal advantage of the possible advantages of the various regimens discussed here.

On the other hand, it is clear that a fair evaluation of new potentially active regimens requires the study of patients with only limited NSCLC; otherwise, the results will probably continue to be biased towards pessimistic conclusions and useful combinations might pass unrecognized. Although there are indications that an improved response rate in

NSCLC can be translated into improved survival [2, 3, 26, 27], further studies should assess whether the regimens discussed here, and which are indeed associated with a 60% response rate, are really superior in terms of survival.

Finally, the future of neo-adjuvant therapy in NSCLC remains unsettled. That surgery is feasible in many patients who respond to neo-adjuvant CT has been established. Whether the combination of neo-adjuvant CT and surgery, with or without radiotherapy, will significantly prolong the survival, for a significant number of patients, can only be answered by controlled studies. The presently available information suggests that such studies should be undertaken.

Many questions remain, however: which is the optimal regimen, how many cycles of CT should be given, what is the role of radiotherapy, if any, and what is the appropriate time for its use [28].

Curing patients with NSCLC represents a fantastic challenge since the presently achievable results are poor and the number of patients to be helped is large. The role of combined modality approaches will certainly continue to be an active area of clinical research in the near future; the goal for these investigations remains the development of an active chemotherapeutic regimen for NSCLC.

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