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Perspectives and Commentaries

Therapy of Small Cell Lung Cancer: Anything New?

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(A COMMENT ON: Cantwell BMJ, Bozzino JM, Corris P, Harris AL. The multi-drug resistant phenotype in clinical practice: evaluation of cross resistance to ifosamide and mesna after VP16-213, doxorubicin and vincristine (VPAV) for small cell lung cancer *Eur J Cancer Clin Oncol* 1988, **24**, 123–129. Kleisbauer JP, Vesco D, Orehek J *et al.* Treatment of brain metastases of lung cancer with high doses of etoposide (VP16-213) *Eur J Cancer Clin Oncol* 1988, **24**, 131–135.)

IT IS the purpose of this short review to concentrate on the major issues which have still attracted interest during the 2 past years and to analyze critically the potential values of these contributions [1].

The most widely used drug combinations include traditionally three of the following four drugs: vincristine, doxorubicin, cyclophosphamide or etoposide (VP16). The latter drug is certainly highly effective and its combination with 'standard' regimens such as CMC (cyclophosphamide, methotrexate, CCNU) or VAC (vincristine, adriamycin, cyclophosphamide) clearly increases the complete response rate and, to a lesser extent, the overall survival [2, 3].

Etoposide has been widely used in SCLC recently; as reported by Kleisbauer *et al.* elsewhere in this issue [4], it can induce responses in brain metastases when administered at a moderately high dosage (1500 mg/m^2). Combined with vincristine, it represents a relatively active and relatively non-toxic regimen, suitable for the treatment of patients with extensive disease who would not tolerate more aggressive treatments [5].

In combination with cisplatin [6] or carboplatin [7], etoposide has proven to be a satisfactory first line regimen in SCLC; the response rates are reasonably high: 43% of CRs with cisplatin + etoposide and 29% with carboplatin + etoposide; but the median survivals remain disappointing, especially with carboplatin: 17.5 and 9.5 months respectively.

More exciting, perhaps, is the relatively high response rate to cisplatin + etoposide or cisplatin + vindesine in refractory SCLC; several studies reported response rates varying between 12% and 52% with these regimens [8–11]. This contrasts with the poor response to VAC, an accepted first line treatment for SCLC, in patients who received previously cisplatin + etoposide + vindesine [12]. Whether these observations indicate that cisplatin + etoposide is, intrinsically, more active than VAC or just represents a non-cross-resistant combination, remains to be further investigated. Whatever the answer might be, it should be stressed that the alternation of cisplatin + etoposide with VAC [13] or the simultaneous use of cisplatin + etoposide + doxorubicin + cyclophosphamide [14] have not resulted in dramatically improved results, as both the response and the survival rates remain within the range of what can be achieved with simpler and less toxic regimens. It is understandable therefore that some investigators have attempted to intensify these regimens by adding additional active drugs such as adriamycin or ifosfamide [15, 16]. These investigations have resulted in increased response rates, in the range of 90%, but are still too preliminary for any conclusions

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regarding the survival.

The concept of alternating drug combinations, despite its considerable interest, the prime purpose being to provide different metabolic attacks to a tumor characterized by heterogeneity—and this is true for SCLC—and to suppress drug resistance, has been somewhat disappointing. As a matter of fact, there is no clear demonstration, so far, that any of the drug regimens that we prescribe in SCLC are really non-cross-resistant with the others. These problems are well-illustrated in the paper by Cantwell *et al.*, published elsewhere in this issue [17]. Nevertheless, there are some indications that alternating regimens might be associated with a modestly improved survival in SCLC, at the expense of increased toxicity [18–21]. Actually, this benefit might derive from the multiple drug nature of these approaches rather than from the alternation itself. Multiple drug regimens have been used successfully in non-Hodgkin lymphomas [22] and other neoplastic diseases; a similar approach might be worth trying in SCLC. Our preliminary experience with a seven drug regimen (cyclophosphamide, adriamycin, etoposide, cisplatin, vindesine, methotrexate, vincristine) is encouraging. On the other hand, maintenance therapy has been clearly disappointing and more recent studies confirm that long term survival does not appear to be affected by prolonged maintenance chemotherapy [23].

The evaluation of response to chemotherapy in SCLC remains difficult and controversial; the evaluation of the response rate depends on the intensity of the staging procedures, and quite different response rates may result in an identical duration of survival [24]. Thus, the survival rates, and especially the late survivals, remain the 'golden standard' to which claims of efficacy should be compared. The numbers of long term survivors remain, unfortunately, distressingly low; a conservative figure might be 3%, 4–5 years after the onset of chemotherapy [25, 26]. Moreover, many of these patients are prone to severe complications resulting from chemotherapy (and radiotherapy) or from the underlying conditions that led to the development of SCLC: myelodysplasic syndromes, acute non-lymphoblastic leukemia, serious neurologic disturbances and non-small cell lung cancer (NSCLC) [27–29].

Although highly intensive cytotoxic treatment, combined or not with autologous bone marrow transplantation, did not give any reason for therapeutic optimism a few years ago, numerous studies continued to appear on this line of investigation. Studies of initial intensive therapy have remained disappointing overall. These investigations have been conducted, most often, with increased doses of cyclophosphamide and/or etoposide. Increased rates of response have been reported [30] as well as benefit for patients achieving a complete response [31]. However, all these studies stress the increased morbidity from the intensification and the lack of benefit to the patients in terms of survival [30–33]. Several large studies of late intensification, performed in patients who had responded completely or partially to induction therapy, have been recently reported. The only randomized investigation comparing high dose BCNU + VP16, with autologous bone marrow transplantation (ABMT), to standard doses in patients, who all responded to a complex chemotherapy regimen including most of the active drugs, failed to demonstrate a survival benefit for the intensified patients despite an increased rate of complete response. Moreover, four out of 23 intensified patients died during the procedure [34].

In spite of claims of success from small studies [35, 36], other larger non-controlled investigations do not contribute to optimism. Ihde *et al.* concluded, from their studies, that only a minority of patients with SCLC were likely to benefit from late intensification + ABMT and that, overall, improvement was unlikely over historical controls [37]. Spitzer *et al.* reported that four patients who had achieved a complete response while intensified with ABMT survived 4 years [38]; but these results are not likely to make late intensification plus ABMT (a formidable procedure) achieve a standard place in our armamentarium against SCLC. Thus, recently obtained results with late intensification + ABMT in SCLC unfortunately do not contradict our own previous conclusions about that procedure: 'late dose intensification is not superior to the usually reported results with standard regimens for the treatment of SCLC' [39].

The role of radiotherapy both with regard to prophylactic cranial irradiation and to the chest, as an adjuvant to systemic therapy treatments, has remained controversial. Although prophylactic brain irradiation reduces the rate of clinical central nervous system relapses, it is more than questionable whether it prolongs survival; it is, however, associated with considerable morbidity in long term survivors [28]. Radiotherapy to the primary tumor definitely reduces the rate of local recurrence, but it is also associated with increased acute and chronic morbidity [40]. Two recent controlled studies claimed a benefit from chest irradiation, in addition to chemotherapy, for limited stages of SCLC. Bunn *et al.* reported an increased (81% vs. 43%) complete response rate in irradiated patients, which translated into a statistically significant survival advantage (15.0 months vs. 11.6 months) [41]. Perry *et al.* found that chemotherapy alone

was inferior to chemotherapy associated with or followed by radiotherapy in patients with limited presentations of SCLC: the response rates were 58% and 36% and the median overall responses were 13.6 and 14.6 months, respectively; these were statistically significant differences [42]. These results cannot be neglected; however, one is struck by the marginal level of the differences that have been demonstrated—although they were statistically significant—between the study groups; it would therefore appear difficult to consider these achievements as major improvements in the management of limited SCLC.

Moreover, SWOG reported, in a large study, no effect on survival from radiation therapy or extension of radiation therapy fields, added to chemotherapy in limited SCLC [43], although that study confirmed the well recognized effect of associated radiotherapy on the frequency of chest relapses.

Uncontrolled studies of radiation therapy added to chemotherapy failed to document a beneficial effect either; although chest relapses could be reduced to a 10% figure, overall median survival rates did not exceed 20 months [44, 45], which is disappointing for such a selected group of patients.

Obviously, the concept of limited vs. extended form of a disease such as SCLC is artificial; SCLC is almost always a disseminated disease and results of staging depend heavily on our capability to detect metastases. It is not surprising, therefore, that attempts to control local disease—except in very limited presentations, as will be discussed later—has regularly met with failure.

More aggressive designs of radiotherapy directed more widely than just to the primary tumor have been attempted as well. Upper and lower hemibody radiation has been investigated, in addition to chemotherapy, in limited and extensive SCLC. Response rates were not increased, but, actually, a shorter time to progression with added radiotherapy has been documented, presumably as a result of poorer tolerance to chemotherapy due to extensive radiotherapy. Overall survivals were disappointing: 9.5 months with the combined approach vs. 13.5 months with chemotherapy alone [46].

Similarly, a study of radiation therapy, in addition to aggressive chemotherapy, to all involved sites in the disease, failed to demonstrate any advantage [47]. Response rates in the patients with extensive SCLC were similar for both treatments; however, there was a significant increase in the number of life-threatening thrombocytopenias among the irradiated patients. The median survival was identical in both study groups: 7 months.

Concerning surgery, radical resection has still been attempted for the small fraction of patients (<5%) who are very thoroughly staged as having T1 or T2NOMO disease.

A recent study by Baker *et al.* [48] reports the results of surgery in a limited number of patients who received initially chemotherapy with cyclophosphamide, doxorubicin and VP16. Out of 37 patients, 19 were resected: in two no residual disease was found, in 10 residual SCLC was discovered and in seven NSCLC alone or in combination with SCLC was diagnosed. All these patients survived for impressive periods of time: 7/12 with no residual disease or persisting SCLC survived 24 months and 5/7 with NSCLC survived for 36 months. By contrast, only two out of 16 non-resected (but irradiated) similar patients survived 15 and 31 months, respectively. These are impressive results which have a clear meaning for the understanding of the biology of SCLC. Similar experiments should definitely be continued, although the number of eligible patients might eventually prove to be relatively small. Retrospective studies of surgical resection of SCLC are less optimistic. In a recent study, Østerlind *et al.* found that surgical resection benefited only those patients who could be completely cured, although the survival rate, at 30 months, was only 33% [49]. The lack of difference between the patients resected with residual cancer and those who were operable but were not resected suggested no major benefit from the resection *per se*.

In a retrospective and uncontrolled study, SWOG found that 15 resected SCLC, who afterwards received chemotherapy and radiation therapy, had a median survival of 25 months as compared to 10.5 months found in 247 'controls'; 33 patients with small tumors but no resection had a median survival of 10.0 months [50].

These studies can hardly be contrued as an incentive for routine surgery in limited SCLC; surgery should remain an investigative procedure, which should nevertheless continue to be studied since its implications for the understanding of SCLC biology are considerable.

Is there 'anything new' in the management of SCLC today? The answer is, unfortunately, no! Chemotherapy, despite the introduction of etoposide (VP16), carboplatin and ifosfamide, remains locked into achievements that were available 10 years ago or even earlier. Maintenance chemotherapy, alternating 'non-cross-resistant' combinations and intensive treatments, with the presently available drugs, have failed to improve the prognosis of patients with SCLC.

Adding radiotherapy to chemotherapy is of no help either.

Truly limited disease should definitely be treated with chemotherapy followed by surgery, as the potential for prolonged survival looks realistic.

Therapy of more extensive disease still remains a challenge; despite the failure of early and late intensification programs more aggressive initial multi-drug therapy—which has proven effective in non-Hodgkin lymphomas—might be an attractive approach.

Information derived from biologic studies—both the tumor and the host—as well as the development of new active cytostatic agents look to be the most promising avenues to a more effective control of SCLC.

REFERENCES

1. Smyth JF, Hansen HH. Current status of research into small cell carcinoma of the lung: summary of the second workshop of the International Association for the Study of Lung Cancer (IASLC). *Eur J Cancer Clin Oncol* 1985, **21**, 1295–1298.
2. Hirsch FR, Hansen HH, Hansen M *et al.* The superiority of combination chemotherapy including etoposide based on *in vivo* cell cycle analysis in the treatment of extensive small-cell lung cancer: a randomized trial of 288 consecutive patients. *J Clin Oncol* 1987, **5**, 585–591.
3. Messeih AA, Schweitzer JM, Lipton A *et al.* Addition of etoposide to cyclophosphamide, doxorubicin, and vincristine for remission induction and survival in patients with small cell lung cancer. *Cancer Treat Rep* 1987, **71**, 61–66.
4. Kleisbauer JP, Vasco D, Orehek J *et al.* Treatment of brain metastases of lung cancer with high doses of etoposide (VP16-213). *Eur J Cancer Clin Oncol* 1988, **24**, 131–135.
5. Morgan DAL, Gilson D, Fletcher J. Vincristine and etoposide: an effective chemotherapy regimen with reduced toxicity in extensive small-cell lung cancer. *Eur J Cancer Clin Oncol* 1987, **23**, 619–621.
6. Evans WK, Shepherd FA, Feld R, Osoba D, Dang P, Deboer G. VP-16 and cisplatin as first-line therapy for small cell lung cancer. *J Clin Oncol* 1985, **3**, 1471–1477.
7. Smith IE, Evans BD, Gore ME *et al.* Carboplatin (paraplatin; JM8) and etoposide (VP-16) as first-line combination therapy for small-cell lung cancer. *J Clin Oncol* 1987, **5**, 185–189.
8. Lopez JA, Mann J, Grapski RT *et al.* Etoposide and cisplatin salvage chemotherapy for small cell lung cancer. *Cancer Treat Rep* 1985, **69**, 369–371.
9. Porter LL, III, Johnson DH, Hainsworth JD, Hande KR, Greco FA. Cisplatin and etoposide combination chemotherapy for retractory small cell carcinoma of the lung. *Cancer Treat Rep* 1985, **69**, 479–481.
10. Chiuten DF, Carr DT, Dhingra HM *et al.* Combination chemotherapy with vindesine and cisplatin for refractory small cell bronchogenic carcinoma. *Cancer Treat Rep* 1986, **70**, 795–796.
11. Batist G, Carney DN, Cowan KH *et al.* Etoposide (VP-16) and cisplatin in previously treated small-cell lung cancer: clinical trial and *in vitro* correlates. *J Clin Oncol* 1986, **4**, 982–986.
12. Sculier JP, Klastersky J, Libert P *et al.* Cyclophosphamide, adriamycin and vincristine: an ineffective second-line chemotherapy regimen for small cell lung cancer. *Proc ASCO*, Atlanta, 1987, Vol. 26, 167, No. 726.
13. Stoller RG, Earle MF, Sanzo K, Brunetti M, Jacobs SA. Up front VP-16/*cis*-platinum in small cell lung cancer (SCLC): final report. *Proc ASCO*, Atlanta, 1987, Vol. 6, 167, No. 659.
14. Sculier JP, Klastersky J and EORTC Lung Cancer Working Party. Phase II combination chemotherapy with cisplatin, adriamycin, etoposide and cyclophosphamide in small cell lung carcinoma. *Proc 14th Int Cancer Congress*, Budapest, 1986, Vol. 3, 1001, No. 3849.
15. Humblet Y, Symann M, Bosly A *et al.* Carboplatin in association with VP16-213 and adriamycin for untreated small cell lung cancer patients: a dose escalation study of carboplatin. *Proc ASCO*, Atlanta, 1987, Vol. 6, 178, No. 700.
16. Smith IE, Perren T, Vincent MD, Gore ME, Yarnold JR. Carboplatin, VP16 and ifosfamide intensive chemotherapy for small cell lung carcinoma. *Proc ASCO*, Atlanta, 1987, Vol. 6, 179, No. 705.
17. Cantwell BMJ, Bozzino JM, Corris P, Harris AL. The multi-drug resistant phenotype in clinical practice; evaluation of cross resistance to ifosfamide and mesna after VP16-213, doxorubicin and vincristine for small cell lung cancer. *Eur J Cancer Clin Oncol* 1988, **24**, 123–129.
18. Meyer RJ, Pearlman NW, Siebert PE *et al.* Comparison of alternating to nonalternating chemotherapy regimens for non-small cell lung cancer. *Cancer Treat Rep* 1986, **70**, 711–714.
19. Pedersen Ag, Østerlind K, Vindeløv L *et al.* Alternating or continuous chemotherapy of small cell lung cancer. A 3 armed randomized trial. *Proc ASCO*, Atlanta, 1987, Vol. 6, 185, No. 731.
20. Aisner J. Alternating chemotherapy for the treatment of small cell carcinoma of the lung. *Proc 13th Int Congress of Chemotherapy*, Vienna, 1983, 205/15-205/23, No. SY 70/4.
21. Murray N, Shah A, Wilson K *et al.* Cyclic alternating chemotherapy for small cell carcinoma of the lung. *Cancer Treat Rep* 1985, **69**, 1241–1242.
22. Klimo P, Connors JM. MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. *Ann Intern Med* 1985, **102**, 596–602.

23. Ettinger DS, Mehta CR, Abeloff MD, Ruckdeschel JC, Aisner S. Maintenance chemotherapy versus no maintenance chemotherapy in complete responders following induction chemotherapy in extensive disease small cell lung cancer. *Proc ASCO*, Atlanta, 1987, Vol. 6, 175, No. 689.
24. Klastersky J, Sculier JP, Dumont JP *et al.* Combination chemotherapy with adriamycin, etoposide, and cyclophosphamide for small cell carcinoma of the lung. A study of the EORTC Lung Cancer Working Party (Belgium). *Cancer* 1985, **56**, 71–75.
25. Alberto P, Mermillod B, Joss R *et al.* Etoposide, cisplatin and doxorubicin in patients with small cell lung cancer: tumor response and long term survival. *Eur J Cancer Clin Oncol* 1986, **22**, 701–708.
26. Sculier JP, Klastersky J, Nguyen N *et al.* Polychimio-thérapie du cancer bronchique indifférencié à petites cellules. Résultats à long terme. *Presse Med* 1986, **15**, 830–834.
27. Dang SP, Liberman BA, Shepherd FA *et al.* Therapy-related leukemia and myelodysplasia in small-cell lung cancer. *Arch Intern Med* 1986, **146**, 1689–1694.
28. Twijnstra A, Boon PJ, Lormans ACM, Ten Velde GPM. Neurotoxicity of prophylactic cranial irradiation in patients with small cell carcinoma of the lung. *Eur J Cancer Clin Oncol* 1987, **23**, 983–986.
29. Johnson DH, Porter LL, List AF, Hande KR, Hainsworth JD, Greco FA. Acute nonlymphocytic leukemia after treatment of small cell lung cancer. *Am J Med* 1986, **81**, 962–968.
30. Johnson DH, DeLeo MJ, Hande KR, Wolff SN, Hainsworth JD, Greco FA. High-dose induction chemotherapy with cyclophosphamide, etoposide, and cisplatin for extensive-stage small-cell lung cancer. *J Clin Oncol* 1987, **5**, 703–709.
31. O'Donell MR, Ruckdeschel JC, Baxter D, McKneally MF, Caradonna R, Horton J. Intensive induction chemotherapy for small cell anaplastic carcinoma of the lung. *Cancer Treat Rep* 1985, **69**, 571–575.
32. Wolff SN, Birch R, Sarma P, Greco FA. Randomized dose–response evaluation of etoposide in small cell carcinoma of the lung: a Southeastern Cancer Study Group trial. *Cancer Treat Rep* 1986, **70**, 583–587.
33. Souhami RL, Finn G, Gregory WM *et al.* High-dose cyclophosphamide in small-cell carcinoma of the lung. *J Clin Oncol* 1985, **3**, 958–963.
34. Humblet Y, Symann M, Bosly A *et al.* Late intensification chemotherapy with autologous bone marrow transplantation in selected small cell carcinoma of the lung: a randomized study. *J Clin Oncol* (In press).
35. Jacobs SA, Santicky MJ, Earle MF, Stoller RG. High dose cytoxan, VP-16, *cis*-platinum with total body irradiation, and autologous bone marrow transplant in responsive small cell lung cancer. *Proc ASCO*, Atlanta, 1987, Vol. 6, 167, No. 658.
36. Postmus PE, Mulder NH, De Vries-Hospers HG *et al.* High-dose cyclophosphamide and high-dose VP16-213 for recurrent or refractory small cell lung cancer. A phase II study. *Eur J Cancer Clin Oncol* 1985, **21**, 1467–1470.
37. Ihde DC, Deisseroth AB, Lichter AS *et al.* Late intensive combined modality therapy followed by autologous bone marrow infusion in extensive-stage small-cell lung cancer. *J Clin Oncol* 1986, **4**, 1443–1454.
38. Spitzer G, Farha P, Valdivieso M *et al.* High-dose intensification therapy with autologous bone marrow support for limited small-cell bronchogenic carcinoma. *J Clin Oncol* 1986, **4**, 4–13.
39. Sculier JP, Klastersky J, Stryckmans P, and the EORTC Lung Cancer Working Party (Belgium). Late intensification in small-cell lung cancer: a phase I study of high doses of cyclophosphamide and etoposide with autologous bone marrow transplantation. *J Clin Oncol* 1985, **3**, 184–191.
40. Brooks BJ, Jr, Seifter EJ, Walsh TE *et al.* Pulmonary toxicity with combined modality therapy for limited stage small-cell lung cancer. *J Clin Oncol* 1986, **4**, 200–209.
41. Bunn PA, Jr, Lichter AS, Makuch RW *et al.* Chemotherapy alone or chemotherapy with chest radiation therapy in limited stage small cell lung cancer. A prospective, randomized trial. *Ann Intern Med* 1987, **106**, 655–662.
42. Perry MC, Eaton WL, Propert KJ *et al.* Chemotherapy with or without radiation therapy in limited small-cell carcinoma of the lung. *N Engl J Med* 1987, **316**, 912–918.
43. Kies MS, Mira JG, Crowley JJ *et al.* Multimodal therapy for limited small-cell lung cancer: a randomized study of induction combination chemotherapy with or without thoracic radiation in complete responders; and with wide-field versus reduced-field radiation in partial responders: a Southwest Oncology Group study. *J Clin Oncol* 1987, **5**, 592–600.
44. McCracken JD, Janaki L, Taylor SA, Weiss GB, Crowley J. Concurrent chemoradiotherapy for limited small cell carcinoma of the lung. *Proc ASCO*, Atlanta, 1987, Vol. 6, 167, No. 656.
45. Shank B, Scher H, Hilaris BS, Pinsky C, Martin M, Wittes RE. Increased survival with high-dose multifield radiotherapy and intensive chemotherapy in limited small cell carcinoma of the lung. *Cancer* 1985, **56**, 2771–2778.
46. Brincker H, Hindberg J, Hansen PV. Cyclic alternating polychemotherapy with or without upper and lower half-body irradiation in small cell anaplastic lung cancer. A randomized study. *Eur J Clin Oncol* 1987, **23**, 205–211.
47. Livingston RB, Schulman S, Mira JG *et al.* Combined alkylators and multiple-site

irradiation for extensive small cell lung cancers: a Southwest Oncology Group study. *Cancer Treat Rep* 1986, **70**, 1395–1401.

48. Baker RR, Ettinger DS, Ruckdeschel JD *et al.* The role of surgery in the management of selected patients with small-cell carcinoma of the lung. *J Clin Oncol* 1987, **5**, 697–702.
49. Østerlind K, Hansen M, Hansen HH, Dombernowsky P. Influence of surgical resection prior to chemotherapy on the long-term results in small cell lung cancer. A study of 150 operable patients. *Eur J Cancer Clin Oncol* 1986, **22**, 589–593.
50. Friess GG, McCracken JD, Troxell ML, Pazdur R, Coltman CA, Jr, Eyre HJ. Effect of initial resection of small-cell carcinoma of the lung: a review of Southwest Oncology Group study 7628. *J Clin Oncol* 1985, **3**, 964–968.