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Commentary

Intensive Chemotherapy in SCLC

JEAN KLASTERSKY

Service de Médecine Interne et Laboratoire d'Investigation Clinique H. J. Tagnon, Institut J. Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, 1 rue Héger-Bordet, 1000 Bruxelles, Belgium

(A COMMENT ON: Hüttner J, Wiener N, Quadt C *et al.* A randomized clinical trial comparing systemic radiotherapy versus chemotherapy versus local radiotherapy in small cell lung cancer. *Eur J Cancer Clin Oncol* 1989, **25**, 933–937).

ALTHOUGH considerable progress has been achieved during the past 20 years in the management of small cell lung cancer (SCLC), overall results have been stagnating recently, in spite of many innovative approaches. Multiple drug therapy has been a milestone in the management of SCLC; it is clearly superior to single drug treatment and to radiotherapy, even if the latter is extensive, as shown in the paper by Hüttner *et al.*, published in this issue [1].

Since SCLC is a tumor responsive to chemotherapy, several attempts have been made to treat SCLC with therapies that have been successful in other sensitive tumors. Among them, the use of a high dosage of chemotherapy and the administration of alternating 'non-cross-resistant' (NCR) regimens have been extensively investigated. Both approaches have a sound biological basis supporting their clinical use.

Many tumors have a steep dose–response curve, making dosage increase a potentially successful procedure; with the help of autologous bone marrow transfusion (ABMT), the hematological toxicity may be bypassed and further dose escalation can be undertaken. Based on a mathematical model, Goldie and Coldman [2] have suggested that the administration of two chemotherapy regimens in a rapid alternating fashion could maximize therapeutic benefit. This approach is often cited as NCR chemotherapy. Unfortunately, the expectations of neither approach are confirmed by clinical investigations so far.

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Intensive chemotherapy in SCLC, with the use of ABMT, has been reviewed recently [3]. At least nine studies have addressed the question of late intensive chemotherapy with ABMT in SCLC patients [3–11]. The results have been disappointing overall, taking into account the fact that most patients included in these studies have been carefully selected for the presence of favorable prognostic factors. In addition, it should be emphasized that the whole procedure of intensive chemotherapy with ABMT is a formidable one, leading to prolonged hospitalization and severe morbidity. These aspects are especially important to consider in view of the disappointing end-term results. In the 178 patients included in these studies, 66 (37%) had a complete response after the procedure; however, only 17 (9.5%) were alive 1 year after therapy and 14 (7.8%) died during the treatment. It should be stressed that many of these patients had achieved only a PR with conventional induction chemotherapy prior to intensification. In a very limited study (five patients), where only patients in complete remission were treated [11], the treatment related mortality was 0% and the one year survival was 20%. It is therefore possible that late intensive therapy might prove to be beneficial only in patients in whom a major reduction of the tumor mass could be achieved through conventional chemotherapy. Although new developments, such as the use of recombinant granulocyte–macrophage colony stimulating factor, might allow for intensive chemotherapy without the burden of ABMT, today late intensive chemotherapy in SCLC must clearly be viewed as an experimental rather than a conventional procedure. It is of particular interest that

the only controlled study comparing late intensive chemotherapy with ABMT to conventional treatment [9] has failed to demonstrate a benefit from the more intensive procedure.

There are few data about initial intensive chemotherapy [12, 13]; although high response rates can be achieved, the overall outcome does not appear to be modified. Once again, this demanding procedure, which compromises the quality of life, is not appealing for patients whose survival is not significantly modified by a treatment.

It remains a fact that, as new more active chemotherapeutic agents or treatments will be developed, the role of early or late intensive therapy in SCLC will require further evaluation.

Between 1981 and 1986, there were eight randomized trials evaluating NCR chemotherapy in SCLC [14]. The results of these studies have not been very encouraging as none has demonstrated a major benefit in long term survival. More recent studies are summarized in Table 1 [15–22]. It appears that alternating therapies result, in most of these studies, in an increased response rate as compared to 'standard' treatment, although sometimes the difference was not statistically significant; however, no difference was found as far as survival is concerned.

Among these studies, two large trials by the National Cancer Institute of Canada [15, 16] attempted to confirm the Goldie and Coldman hypothesis; however, their results in favor of the alternating regimen can be explained merely by the fact that cisplatin (P) + etoposide (E) is a drug combination superior to cyclophosphamide + Adriamycin® + vincristine (CAV). As a matter of fact, the study by Fukuoka *et al.* [21], confirms that PE is superior to CAV in terms of response and although CAV–PE alternation is better than CAV, it is not superior to PE.

Moreover, it should also be stressed that most, if not all, of these studies have failed to provide evidence that the alternated regimens were really NCR, a prerequisite in the Goldie and Coldman hypothesis. Even CAV and PE do not fulfil this requirement: whereas approximately 50% of the patients will respond to PE following CAV, patients previously treated with PE have a poor response to CAV [23].

In another large study, by Havemann [17], the combination of etoposide, vindesine and ifosfamide alternated with CAV, was significantly superior to CAV. Once again there is no proof that the two regimens were NCR; on the other hand, ifosfamide and etoposide are active in SCLC, and might prove more active than CAV, in the future.

It remains nevertheless the case that, in most of the recent studies in which drug combinations have been alternated, a superior response rate was found with the multiple drug regimen. This is confirmed by the study of Hüttner *et al.* [1], already mentioned; the alternation of POCC (procarbazine, vincristine, cyclophosphamide and lomustine) with VAM (etoposide, doxorubicin and methotrexate) resulted in a median survival in patients with extensive disease that fits in well with the best reported results in the literature. Whether this is due to the alternation or to the use of more potent drugs in the alternating active arm remains to be seen; the use of a multiple drug regimen *per se* may represent the explanation for this modestly improved activity. In other tumors,

Table 1. Alternating regimens in SCLC—recent controlled studies

References	Number of patients	Standard therapy (S)*	Alternating regimen (A)*	Response rate %(CR)			Median survival (months)	
				S		A	S	A
Evans [15]	289	CAV	CAV–PE	63 (27)	($P < 0.002$)	80 (39)	8.0	9.6
Feld [16]	300	CAV	CAV–PE	78 (44)	($P = 0.2$)	82 (52)	15.0	16.3
Havemann [17]	306	CAV	CAV–EVil	59 (21)	($P < 0.05$)	70 (36)	10.0	11.3
De Marinis [18]	44	EpV	CEpV–PE	75 (?)	NS	83 (?)	14.5	12+
Boni[19]	82	PE	PE–CAV–CCnVM	95 (49)	($P = 0.03$)	73 (24)	—	—
Camacho [20]	18	CAV	PEM	56 (11)	NS	67 (44)	8.0	10.0
Fukuoka [21]	257	CAV	CAV–PE	55 (10)	($P < 0.01$)	77 (13)	11.8	12.0
		PE	CAV–PE	81 (12)	NS	77 (13)	11.5	12.0
Fukuoka [22]	65	CVAcPr	CVAcPr–CAE	64 (17)	($P < 0.1$)	83 (32)	9.2	9.4

*C = cyclophosphamide; A = doxorubicin; V = vincristine; P = cisplatin; E = etoposide; Ep = epidoxorubicin; Ac = ACNU, nimustine; Pr = procarbazine; M = methotrexate; Cn = CCNU, lomustine; Vi = vindesine; I = ifosfamide.

Table 2. Intensive weekly chemotherapy for SCLC

References	Number of patients	Chemotherapy* (scheduling: days if not otherwise specified)	Response rate (%)		Survival	
			CR	PR	Median	>2 year
Miles [24]	21	PE-IA (weekly alt.)	3 (15%)	19 (90%)	—	—
Williamson [25]	50	CA(1), M(8), P(15), E(15–17), V(8, 22)	18 (37%)	42 (85%)	—	—
Wampler [26]	12	EP–PV–CA–M (weekly alt.)	5 (42%)	10 (83%)	—	—
Twelves [27]	23	IVi (weeks 0, 2, 4), EP (weeks 6, 9, 12), AM (weeks 15, 17)	10 (43%)	21 (91%)	13, 5	30%
Institut J. Bordet [28]	21	CAV(1), PE(8), MVi(15)	4 (19%)	15 (71%)	—	—
Total	127		40 (31%)	107 (84%)	—	—

*C = cyclophosphamide; A = doxorubicin; V = vincristine; P = cisplatin; E = etoposide; Pr = procarbazine; M = methotrexate; Vi = vindesine; I = ifosfamide.

namely the poor prognosis non-Hodgkin's lymphomas, multiple drug regimens have proven to be highly efficacious.

Several recent studies have investigated the very specific question of whether intensive weekly multidrug chemotherapy might be active in SCLC. These investigations are summarized in Table 2 [27–28]. Although these investigations are still limited, it is striking to observe that the complete response rates and the overall response rates are very high in these series; all these studies concluded that the intensive regimens were well tolerated and highly effective. As a matter of fact, several controlled trials of multidrug weekly chemotherapy in SCLC versus conventional therapy have now begun [24, 26, 28].

Thus, the simultaneous combination of many active drugs, or the rapid rotation of active regimens, might provide for SCLC patients a new intensive approach. Its feasibility seems to be easier than that of intermittent high dose chemotherapy that results in severe bone marrow suppression; as a consequence, the quality of life of the patients appears to be better preserved.

SCLC is far from being controlled today and, in spite of new agents such as cisplatin, etoposide and ifosfamide, no major progress has been made recently. This might have to do with the way we use the available agents either quantitatively or qualitatively. There are indications that multiple drug regimens that are rapidly rotated in order to result in an intensive, but still easily feasible therapy, might be associated with promising results. This approach, which combines the concepts of intensive chemotherapy with that of alternation of drugs, and which has already proven to be effective in other tumors, certainly deserves further investigation.

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