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Acknowledgement—I would like to thank Mrs M. Paesmans and Drs T. Berghmans, C. Castaigne, S. Luce, C. Sotiriou and P. Vermylen for their help in the qualitative assessment of the trials.

PII: S0959-8049(98)00082-3

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SMALL CELL lung cancer (SCLC) remains a therapeutic challenge, despite the fact that this neoplasm shares many of the features of other tumours curable by chemo- and radiotherapy, such as rapid progression, short doubling time, sensitivity to multiple chemotherapeutic agents and radiation therapy. The introduction of combination chemotherapy into the management of SCLC has resulted in a high overall remission rate, a considerable rate of complete remissions, a 4- to 5-fold prolongation of median survival and a small proportion of patients surviving disease-free over a period of more than 2 years. However, the majority of patients will ultimately relapse and succumb to their disease. In order to prolong remission duration, survival and possibly the number of long-term survivors ('cures'), several types of maintenance therapy have been used: chemotherapy/high-dose chemotherapy; consolidating radiotherapy; biological response modifiers, such as interferons, anticoagulants, etc.

This paper will be restricted to the discussion of maintenance chemotherapy. For the purpose of this discussion, we will use the term 'maintenance chemotherapy' as cytostatic treatment after achieving a maximum tumour response in an individual patient with a given induction therapy. From the above, it is already evident that the value of maintenance chemotherapy might be different in patients with complete versus partial response after induction chemotherapy and in patients with limited versus extensive disease.

CONVENTIONAL DOSE MAINTENANCE CHEMOTHERAPY

The term 'maintenance' chemotherapy was introduced in 1960, when it was recognised that chemotherapeutically-induced complete remissions in acute lymphocytic leukaemia were short lived in the absence of treatment during remission, and that it could be prolonged by such treatment, that is, so-called maintenance treatment [1]. In general, maintenance chemotherapy is delivered at relatively conservative doses. Although maintenance treatment for the leukaemias and lymphomas has usually been demonstrated to prolong the duration of remission, there is no clear evidence from any study that maintenance treatment will increase the cure rate. Indeed, the original goal of maintenance treatment was not directed towards cure, but rather at prolonging the time to relapse.

Indirect evidence for the ineffectiveness of maintenance chemotherapy in SCLC stems from several non-randomised trials and a number of randomised trials discussed below. In two consecutive Canadian studies, the value of maintenance chemotherapy was tested in a non-randomised manner. In the first trial performed by Feld and coworkers, 161 patients underwent three cycles of induction chemotherapy with cyclophosphamide, doxorubicin and vincristine, followed by radiation therapy to the primary and the mediastinum. Thereafter, maintenance chemotherapy with lomustine (CCNU), methotrexate and procarbazine was given over 1 year [2]. In a consecutive study, the same group treated 320 patients with six cycles of induction chemotherapy with cyclophosphamide, doxorubicin and vincristine with consolidating radiotherapy [3]. No maintenance chemotherapy was given in this trial. Median survival in both trials was identical.

Aside from this indirect evidence, at least 13 randomised trials testing the value of maintenance chemotherapy have been performed (see Table 1) [4–16]. Unfortunately, most trials entered only a small number of patients into the maintenance part of the study, so that the statistical validity of the conclusions is rather limited. However, 11 of 13 trials found no significant overall difference in survival. Subset analysis in the large trial of Bleehen and coworkers showed that in 99 patients who had a complete response to initial chemotherapy as assessed at the time of randomisation, there was a suggestion that survival was longer in the maintenance chemotherapy arm, the median survival from the date of randomisation being 42 weeks for the maintenance and 30 weeks for the no maintenance patients ($P < 0.05$, log rank test). However, maintenance chemotherapy was associated with additional toxicity and a poorer quality of life, as assessed intermittently by clinicians and daily by patients. The authors concluded that 'no worthwhile clinical advantage was achieved by maintenance chemotherapy' [6]. Furthermore, the two trials showing some benefit for maintenance chemotherapy did so only for patients with extensive disease [8, 13]. In addition, it is of interest that the large trial of Giaccone and coworkers

Table 1. *Randomised trials of maintenance versus no maintenance chemotherapy*

Induction chemotherapy	Maintenance chemotherapy	Number of patients	Survival	Statistical significance	Comment	Authors
CCNU/CTX/VCR/MTX×6	CCNU/CTX/VCR/MTX	6	–	n.s.	Trial too small!	Bakker and colleagues [4]
	versus				Decreased quality of life with maintenance chemotherapy!	
	no maintenance	6				
VP/DDP	CTX/DOX/VCR	129	53 weeks	n.s.	No significant difference in overall survival or disease-free survival	Beith and colleagues [5]
VP/CTX/MTX/VCR×6	VP/CTX/MTX/VCR×6	131	35 weeks*	n.s.	Maintenance chemotherapy was associated with additional toxicity and a poorer quality of life!	Bleehen and colleagues [6]
	versus					
	no maintenance	134	29 weeks*			
DDP/VP–CTX/VCR/MTX×3	CTX/VCR/MTX×6	33	14.1	s.s.	Maintenance chemotherapy deleterious!	Byrne and colleagues [7]
	versus					
	no maintenance	35	19.2			
DOX/CTX/VCR×6	DOX/CTX/VCR×8	45	–	See comment	Significant survival advantage with maintenance for ED patients (372 days versus 259 days, $P = 0.006$)	Cullen and colleagues [8]
	versus					
	no maintenance	48				
CTX/DOX/VCR×6	DDP/VP×2	72	97.7 weeks	s.s.	This trial is testing consolidation chemotherapy with a non-cross-resistant regimen, but no maintenance therapy	Einhorn and colleagues [9]
	versus					
	no further treatment	76	68 weeks			
CTX/DOX/VCR ± HMM/VP/MTX×6–8	CTX/DOX/VCR ± HMM/VP/MTX	Total: 577		See comment	ED only! Maintenance beneficial after CTX/DOX/VCR-induction, but not after CTX/DOX/VCR ± HMM/VP/MTX	Ettinger and colleagues [10]
	versus	Maintenance: 79				
	no maintenance					
CTX/DOX/VP×5	CTX/DOX/VP×7	434	326 days	n.s.	Prolonged chemotherapy offers no better chance for cure and does not prolong survival	Giaccone and colleagues [11]
	versus					
	no maintenance					
CCNU/CTX/DOX/VP×6	CCNU/CTX/DOX/VP	Total: 320	479 days	n.s.	Only CR patients randomised to maintenance phase	Lebeau and colleagues [12]
	versus	Maintenance: 79				
	no maintenance		393 days			
CTX/MTX/VCR	CTX/MTX/VCR	18	16.8 months	s.s.	258 patients entered into the trial. No difference between maintenance versus no maintenance in LD in CR	Maurer and colleagues [13]
	versus					
	no maintenance	18	6.8 months			
CTX/DOX/VCR	VP	17	9 months	n.s.	103 patients entered into the trial, 34 patients with limited disease in CR randomised to maintenance arm	Niederle and colleagues [14]
	versus					
	no maintenance	17	8 months			
IFOS/VP/DOX or EPI-DOX	VP/VDS	42	48 weeks	n.s.	Maintenance chemotherapy in responding patients is beneficial	Sculier and colleagues [15]
	versus					
	no maintenance	42	38 weeks			
CTX/VCR/VP×4	CTX/VCR/VP×4	305	39 weeks	n.s.	Survival equivalent only, if second-line chemotherapy given to patients with short induction chemotherapy	Spiro and colleagues [16]
	versus					
	no maintenance	305	32 weeks			

*Survival from allocation to maintenance chemotherapy versus no maintenance. CCNU, lomustine; CTX, cyclophosphamide; VCR, vincristine; MTX, methotrexate; VP, etoposide; DDP, cisplatin; DOX, doxorubicin; HMM, hexamethylmelamine; IFOS, ifosfamide; EPI-DOX, 4'Epi-doxorubicin; n.s., not significant; s.s., statistically significant; ED, extensive disease; CR, complete remission; LD, limited disease.

Table 2. Results of high-dose chemotherapy with ABMT

Intensive consolidation		Standard consolidation	*P* value
34 weeks	Median response time* for extensive disease patients	10 weeks	Not specified
42 weeks	Median survival for extensive disease patients	40 weeks	Not specified
42 weeks	Median response time* for limited disease patients	8 weeks	< 0.005
104 weeks	Median survival for limited disease patients	62 weeks	< 0.05

*Median response time, time between randomisation and relapse.

with no dose reduction for the maintenance chemotherapy did not show any advantage in survival or cure rate for five versus 12 cycles of a combination chemotherapy regimen with cyclophosphamide, doxorubicin and etoposide [11]. Finally, the CRC trial illustrated the relevance of appropriate treatment at relapse if only a short induction chemotherapy is given. The authors concluded that 'the policy of stopping treatment early will lead to earlier relapse. In the group as a whole no survival disadvantage results provided chemotherapy is given on relapse' [16].

From these data, it appears that in SCLC the value of conventional maintenance chemotherapy is marginal or non-existent in patients with limited disease achieving a complete remission after induction chemotherapy given for five to six cycles. From the limited data available, there is a suggestion that maintenance chemotherapy will prolong remission duration and survival in extensive disease patients, but at the cost of additional toxicity and a poorer quality of life.

HIGH-DOSE MAINTENANCE CHEMOTHERAPY/ LATE INTENSIFICATION

In order to achieve optimal results with chemotherapy, it is necessary to achieve a certain level of toxicity, i.e. a predictable and reversible decrease in haematological parameters, with a median leucocyte nadir of approximately 1,000–1,500/mm^3 [17]. Data from animal as well as clinical studies have shown, for a broad variety of cytostatic agents, a relationship between dose or dose intensity over time and response [18]. Assuming the clinical value of a steep dose–response relationship, several groups have taken a radical approach by increasing the doses of chemotherapy to the limits of extramedullary toxicity and reconstituting normal haematopoiesis by autologous bone marrow transplantation (ABMT). There have been two basic study designs for the application of high-dose chemotherapy with autologous bone marrow rescue. One approach is the induction of a remission with standard dose chemotherapy and, thereafter, 'consolidation/late intensification' with high-dose chemotherapy with ABMT. The second approach, which is beyond the scope of this discussion, is to use high-dose chemotherapy with ABMT upfront as induction chemotherapy. Several excellent reviews have been published on the use of high-dose chemotherapy with ABMT [19–21]. Unfortunately, most of the data currently published are derived from small pilot series with selected groups of prognostically favourable patients, so that no firm conclusions can be drawn about the effectiveness of this approach. One exception, however, is a randomised trial of intensive consolidation chemotherapy with ABMT after standard dose induction with a non-cross-resistant induction chemotherapy [22]. 98 patients received three cycles of vincristine 1.5 mg/m^2, cyclophosphamide 600 mg/m^2, doxorubicin 60 mg/m^2 and methotrexate 40 mg/m^2, all given intravenously (i.v.) at 3 week intervals followed by prophylactic brain irradiation combined with two courses of cisplatin 80 mg/m^2 i.v. and etoposide 120 mg/m^2 i.v.$\times$3. After re-evaluation, limited disease patients with a complete or partial response and extensive disease patients with a complete response, were randomly assigned to either intensive consolidation therapy or one additional cycle of conventional dose chemotherapy. Intensive consolidation consisted of cyclophosphamide 6 g/m^2 i.v. over a period of 4 days, etoposide 500 mg/m^3 i.v. over 4 days, and carmustine (BCNU) 300 mg/m^2 i.v. followed by ABMT. Conventional dosages were cyclophosphamide 750 mg/m^2 i.v., etoposide 120 mg/m^2 orally for 5 days and BCNU 60 mg per m^2 i.v. The overall response rate to induction treatment was 77% with 33% of limited disease and 18% of extensive disease patients achieving a complete remission. 38 of the 98 patients (39%) were randomised after induction therapy to consolidation treatment with standard or high-dose chemotherapy with ABMT (see Table 2).

Among the 12 autografted limited disease patients, 5 had relapsed at the time of the preliminary report with 4 patients relapsing in the chest (chest radiotherapy was not used in this trial).

In summary, very high-dose chemotherapy with ABMT may improve the results in a small number of selected patients. Further randomised trials with improved methodology (peripheral stem cell support, bone marrow purging, addition of new active drugs with limited extramedullary toxicity, etc.) are needed in order to define the ultimate place of this resource consuming approach in the treatment of SCLC.

CONCLUSIONS—THE ARGUMENTS AGAINST MAINTENANCE CHEMOTHERAPY

After achieving a maximum tumour response with a standard induction chemotherapy regimen given for five to six cycles, there is no convincing evidence that prolonged maintenance chemotherapy in conventional dosages is beneficial in patients with SCLC. There is some suggestion that conventional maintenance chemotherapy in extensive disease patients may prolong relapse-free survival and overall survival, but at the cost of increased toxicity and decreased quality of life. Whether consolidating high-dose chemotherapy with peripheral stem cell support or ABMT can increase the cure rate in limited disease patients in complete remission, remains to be proven.

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PII: S0959-8049(98)00083-5

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THE DURATION of chemotherapy in patients with small cell lung cancer (SCLC) has been debated for many years, and for many years the 'standard' length of treatment was 12–18 months. More recently, several randomised studies have demonstrated that 4–6 months of treatment is equal to prolonged treatment when survival time is considered as the final endpoint.

The major limitation of treatment in SCLC is the relatively short duration of response due to the occurrence of chemoresistant tumour cells. Several treatment approaches to overcome resistant mechanisms have been tested, including the 'maintenance therapeutic approach', which in most cases consists of maintenance chemotherapy, i.e. cytostatic treatment after achieving a maximum tumour response in an individual patient with a given induction therapy. The topic is still under debate and is in this issue discussed by Dr Sculier (pro) and Drs Joss and Schefer (contra). Both articles contain a critical review of published studies and focus on both conventional dose of chemotherapy and high-dose maintenance chemotherapy/late intensification. In addition, they describe several important methodological problems in the design of such studies, with subsequent implications for the interpretation of the results. The groups of patients receiving maintenance chemotherapy are very heterogenous. In some studies, only patients in complete remission went on to receive maintenance therapy, while in other studies both patients in complete and partial remission were treated. In other studies, patients with stable disease have also been included. Another problem is that the induction chemotherapy used in most of the early studies from the 1980's must be considered inferior treatment today because many of them did not include platinum and etoposide. After the publication of most of the reports, the routine use of chest irradiation has been introduced for patients with limited disease, resulting in