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Current Controversies in Cancer

Should Maintenance Chemotherapy be used to Treat Small Cell Lung Cancer?

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THE ADMINISTRATION of active combination chemotherapy has resulted in a major advance in the treatment of small cell lung cancer (SCLC). However, only a minority of patients can be considered cured: the overall 5-year survival rate is approximately 5–10% and there are 10 times more long-term survivors among patients with limited disease than in those with disseminated cancer. Among the various attempts to improve these results, intensive chemotherapy has been and still is, the subject of many randomised trials. Other means of improving results have involved increasing the number of active drugs in the combination or the dosage of one or several of the administered agents, reducing intervals between courses of chemotherapy and augmenting the total duration of the treatment by providing a maintenance or consolidation therapy.

Maintenance chemotherapy is a controversial topic. Prolongation of the duration of chemotherapy is considered by most investigators to have no influence on patient survival and, therefore, not to be useful in SCLC. Administration of approximately six courses of chemotherapy is often considered the standard treatment. In fact, that attitude is mainly based on a retrospective analysis [1], but is not supported by the results of all published prospective randomised trials.

Since 1980, 13 randomised trials [2–15] have been published, having as one of their endpoints the evaluation of a maintenance chemotherapy after an induction regimen. They are summarised in Table 1. One study [4, 5] showed a statistically significant difference in survival in favour of maintenance, five reported some survival advantages in subgroups of patients [2, 3, 6, 7, 14], one [12] showed a significant shorter survival with maintenance and in six studies [9–13, 15], there was no difference between both arms. Usually the effect on disease-free survival is similar, but we will not consider this point in our discussion, because the data are not available in all studies, although it can be important for quality of life. Results are, thus, not uniformly negative and a critical look at the studies is necessary to find explanations why maintenance therapy might improve survival in some circumstances.

A quantitative overview or meta-analysis could be helpful for determining, by appropriate statistical analysis, if a global beneficial effect of maintenance therapy is found when the trials are aggregated. This approach will not provide definitive conclusions, but can give an indication for further controlled confirmatory studies.

Unfortunately, the lack of available data and the heterogeneity of the published studies prevent a meaningful meta-analysis.

A qualitative assessment of the randomised trials can determine if some are better and, thus, should be given more weight. Chalmers and colleagues [16] described a score which evaluated two dimensions of quality: the internal (scientific) and external (generalisability of results) validities, with, respectively, 11 and 5 items. Table 2 reports the Chalmers quality scores calculated for the 13 randomised trials according to the information provided by the publications. When the trials that showed no advantage for maintenance therapy were compared according to this score with those that obtained some survival advantage, there was no significant difference in score rates between both groups, with respective mean rates of 47 and 45% for the 'negative' and 'positive' studies (non-parametric test, $P = 0.62$). It should be noted that there exists a very significant time effect, the earliest studies having lower scores than the latest (correlation coefficient $r = 0.76$; $P < 0.001$). The absence of significant differences in scores between the 'negative' and 'positive' trials indicates that they can be considered of a similar quality and thus handled in the same way.

Table 1. *Summary of randomised trials evaluating the role of maintenance chemotherapy*

First author, year [ref.]	Population randomised	Induction regimen		Maintenance regimen		No of randomised patients	PFS	Survival
		Drugs	No. of courses	Drugs	No. of courses			
Maurer, 1980 [2]	Complete responders	CPA or CPA-MTX-VCR	6	cf induction	Until relapse	47	NS	(S)
Cullen, 1986 [3]	Objective responders	CPA-ADR-VCR	6	cf induction	8	61	?	(S)
Einhorn, 1988 [4] Johnson, 1993 [5]	Objective responders	CPA-ADR-VCR	6	CDDP-VP16	2	151	S	S
Bleehen, 1989 [6]	Objective responders	VP16-CPA-MTX-VCR	6	cf induction	6	265	?	(S)
Spiro, 1989 [7]	Initially	CPA-VCR-VP16	4	cf induction	4	610	S	(S)
Byrne, 1989 [8]	Initially	CDDP-VP16/CPA-VCR-MTX	3×2	CPA-VCR-MTX	6	66	NS	SN
Ettinger, 1990 [9]	Complete responders	CPA-ADR-VCR ± HMM-VP16-MTX	6–8	cf induction	20–22	86	(S)	NS
Mattson, 1992 [10]	Objective responders	CPA-VCR-VP16 + RT	4	CPA-CDDP-ADR	6	146	?	NS
Lebeau, 1992 [11]	Complete responders	CCNU-CPA-ADR-P16	6	cf induction	6	79	NS	NS
Giaccone, 1993 [12]	Non-progression	ADR-VP16-CPA	5	cf induction	7	434	S	NS
Bleehen, 1993 [3]	Initially	VP16-CPA-MTX-VCR	3	cf induction	3	309	?	NS
Sculier, 1996 [14]	Objective responders	Ifo-VP16-ADR or epirubicin	6	VP16-VDS	12	91	S	(S)
Beith, 1996 [15]	Objective responders	VP16-CDDP + RT	4	ADR-CPA-VCR	10	129	NS	NS

NS, not statistically significant; S, significant; (S), significant in subgroup; SN, significant not in favour of maintenance; PFS, progression-free survival; CPA, cyclophosphamide; VCR, vincristine; MTX, methotrexate; ADR, doxorubicin; CDDP, cisplatin; HMM, hexamethylmelamin; Ifo, ifosfamide; RT, thoracic irradiation; VDS, vindesine.

Table 2. Chalmers' quality score for randomised trials assessing maintenance chemotherapy in small lung cancer [16]

First author, year [ref.]	Internal validity (%)	External validity (%)	Total score (%)
Maurer, 1980 [2]	22	14	20
Cullen, 1986 [3]	15	34	27
Einhorn, 1988 [4] } Johnson, 1993 [5] }	47	41	46
Bleehen, 1989 [6]	50	34	46
Spiro, 1989 [7]	58	41	53
Byrne, 1989 [8]	53	41	49
Ettinger, 1990 [9]	14	34	19
Mattson, 1992 [10]	40	34	39
Lebeau, 1992 [11]	71	41	63
Giaccone, 1993 [12]	52	41	49
Bleehen, 1993 [13]	69	25	59
Sculier, 1996 [14]	91	48	77
Beith, 1996 [15]	57	48	55

There are only two trials (23%) that defined, as the primary endpoint, the effect of maintenance therapy on overall or disease-free survival with an a priori estimate of the number of patients required to perform a comparison with an adequate power at a low risk of type I error. Both reported with some advantage in favour of the experimental (maintenance) arm [7, 14]. All the trials that did not demonstrate a statistical difference, may not have had the statistical power to show such a difference, since there was no a priori statistical estimates made of patient numbers required. For the 'positive' studies, the conclusions can only be considered as definitive if the significance test concerned the primary endpoint as defined in the statistical considerations. This is the case for the study by Spiro and colleagues [7] for overall survival and for our study for disease-free survival [14].

If the studies are compared for their design concerning the maintenance therapy question, taking into consideration the type of patients randomised (response status, disease extent), the regimens used for induction and maintenance (drugs, number of courses) and the moment of randomisation, none of the trials showing some survival advantage have a counterbalancing negative one with similar design characteristics.

For all of these reasons, the advantages observed in the positive trials have to be considered, at least for planning new controlled studies, if not in clinical practice. The positive effects of maintenance are: (a) The continuation of therapy in patients with either: limited disease and a complete response obtained by cyclophosphamide alone or in combination with methotrexate and vincristine [2]; extensive disease and an objective response with a vincristine–doxorubicin–cyclophosphamide regimen [3]; or those having a complete response after a combination of etoposide, cyclophosphamide, methotrexate and vincristine [6]. (b) With this latter regimen, treatment should not be limited to four courses, but continued for at least eight courses [7]. (c) In the case of a complete response after induction by vincristine, doxorubicin and cyclophosphamide, two further courses with cisplatin and etoposide should be considered [4, 5], as well as 12-course therapy with etoposide and vindesine in responders to a regimen containing ifosfamide, etoposide and a high-dose intensity of an anthracycline.

Finally, there is one trial showing a statistically significant decreased survival with maintenance therapy—a combination of cyclophosphamide, vincristine and methotrexate after induction therapy of alternating the same regimen with cisplatin plus etoposide [8]. The interpretation of these results should be cautious, because this trial is the smallest one (66 patients registered initially), it has a relatively smaller quality score, it was performed by a relatively limited number of centres and there were no valid statistical considerations in the report. The conclusions are, thus, equivocal.

In conclusion, if the literature is reviewed with an adequate methodology, there is so far no demonstration by a valid study that maintenance chemotherapy has no role in SCLC. On the contrary, there are some trials supporting its use, but, because of a methodology that is often weak, confirmation is needed by adequate controlled studies in order to avoid any further discussion.

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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