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Maintenance chemotherapy for anaplastic small cell carcinoma of the bronchus: A randomised, controlled trial*

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Summary. Since March 1980, 309 patients with anaplastic small cell carcinoma of the bronchus (ASCB) have received remission induction therapy prior to randomisation to maintenance (M) or no maintenance (NM) chemotherapy. Induction therapy consisted of six courses of vincristine, doxorubicin and cyclophosphamide (VAC) given IV every 3 weeks. Those with limited disease also received mediastinal irradiation. Consenting patients with no unequivocal residual disease were randomised to have no further treatment until relapse or a further eight courses of VAC, at a lower dosage, every 4 weeks. Patients failing to achieve randomisation status received palliative treatment only. The median survival for all patients with limited disease (LD) is 363 days and that for patients with extensive disease (ED) is 272 days ($P < 0.00001$).

Sixty-one patients with ED were randomised. Those having maintenance chemotherapy lived significantly longer (median 372 days) than those who did not continue therapy (median 259 days) ($P = 0.006$). An imbalance in the proportion of 'complete remitters' randomised to maintenance therapy does not account for this difference. There is no significant difference between the M and NM groups in the 32 randomised LD patients. Continuing treatment during remission with agents used to induce the remission can prolong survival in patients with extensive stage ASCB.

Introduction

Chemotherapy has been the mainstay of treatment for anaplastic small cell carcinoma of the bronchus (ASCB) for more than a decade. Nevertheless, there is no clear indication of how long chemotherapy should continue in patients who achieve remission. On the one hand, it is well known that almost all patients will relapse and die from the disease. Consequently, many centres continue treatment during remission in the hope of delaying that event [2, 5]. On the other hand, there are reports of prolonged unmaintained remissions in this disease [6]. Thus, in March 1980, a randomised, multicentre trial was set up in the Midlands to answer the question: In patients with ASCB who respond to chemotherapy, does maintenance chemotherapy prolong survival?

Patients and methods

Patients 70 years of age and under, with histologically or cytologically proven ASCB, were classified as having limited or extensive stage disease according to the following criteria:

Limited disease (LD). Tumour was apparently confined to one hemithorax; no patients with cervical lymphadenopathy, pleural effusion, or abnormal liver function tests were admitted to this classification. These patients were all required to have normal isotope bone scan, liver scan and bone marrow aspiration.

Extensive disease (ED). Evidence of tumour was found beyond the limits described for LD.

All patients who were not bedridden were eligible for inclusion. Chemotherapy (VAC) consisted of vincristine (1 mg/m^2 to max 2 mg), doxorubicin (40 mg/m^2) and cyclophosphamide (1000 mg/m^2) IV every 21 days. In patients over 65 the doses were: vincristine 1 mg/m^2 (max. 1.5 mg), doxorubicin 30 mg/m^2 and cyclophosphamide 600 mg/m^2. Six courses of induction chemotherapy were given. In addition, patients with LD received radiotherapy (RT) to the involved mediastinal field using megavoltage equipment, to a total dose of 30 Gy in ten fractions over 12 days, starting within 7 days of VAC 1. A similar total dose and fractionation schedule for prophylactic cranial irradiation (PCI) was employed in LD patients who had responded between VAC 3 and 4. After six courses of VAC patients were reassessed for treatment response, with evaluation of all areas previously known to have been involved. Repeat bronchoscopy was not required. The following categories of response were recognised:

Complete response (CR): Disappearance of all clinical, radiological and biochemical evidence of tumour.

Good response (GR): No unequivocal residual disease. These patients had responded very well to treatment but

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had minor residual abnormalities, e.g. slight residual chest X-ray changes or those due to radiation.

Partial response (PR): Greater than 50% reduction in measurable tumour, but with residual disease.

Fail (F): less than 50% reduction in tumour bulk or death during induction therapy.

Only the first two categories of patient were eligible for the randomised trial. Thus, CR and GR patients who were considered not to have experienced excessive toxicity during induction, and who consented, were randomly assigned to receive no further treatment (NM) until relapse or a further eight courses (M) of VAC every 28 days at the following doses (for all ages): vincristine 1 mg/m^2 (max. 1.5 mg), doxorubicin 30 mg/m^2 and cyclophosphamide 600 mg/m^2. Patients were stratified into LD and ED prospectively and randomised separately. Patients who achieved PR, or who failed to respond, received palliative treatment only, as did randomised patients at relapse.

Statistical methods

Survival curves were constructed according to the method of Kaplan and Meier [7], with differences being evaluated using the log-rank test [9]. A stepwise linear regression based on Cox's proportional hazards model [3] was used to allow for any imbalances in factors known to affect survival when the two randomisation groups were compared, and to test for interactions between prognostic variables as they affect survival.

Results

By 1 December 1984, a total of 309 patients had entered the study. These comprised 79 with LD and 230 with ED. Figure 1 compares the survival from the date of first treatment for LD and ED, with medians of 363 days and 272 days, respectively ($P<0.00001$ log-rank test). Entry to the randomised trial was discontinued in August 1983, and treatment response has been assessed in the 275 patients on study at this time (Table 1). Complete or good responses were achieved in 120 patients, who were thus eligible for randomisation. However, 14 patients refused randomisation and 13 were felt to have experienced a level of toxicity from induction therapy that would make randomisation inappropriate. Thus, 93 patients were randomised. Figure 2 compares the survival curves for 61 ED patients who entered the randomised trial. The median survival (from the date of first treatment) is 372 days for the maintenance group and 259 days for the no maintenance group. There is a significant advantage for those receiving maintenance chemotherapy ($P=0.006$). The two groups are well balanced for age and sites of metastatic disease. There are, however, slight imbalances in the proportions of patients with different performance statuses, both before treatment and at randomisation, and in the proportions of CR and GR patients randomised to the two arms (Table 2). The performance status had generally improved by the time of randomisation (Table 2), and consequently survival comparisons are based on ranges of 0–1 vs 2–3 for pretreatment performance status. A Cox multivariate regression including response, randomisation and both pretreatment and randomisation performance status defined in this way showed that the latter two scores correlated independently with survival ($P=0.04$ and 0.08, respectively) and that the difference between the two arms was reduced, but still significant, after allowing for these two factors ($P=0.05$). A trend on univariate analysis for patients attaining CR to survive longer than those achieving only GR ($P=0.1$) was no longer apparent on multivariate analysis ($P=0.84$) after

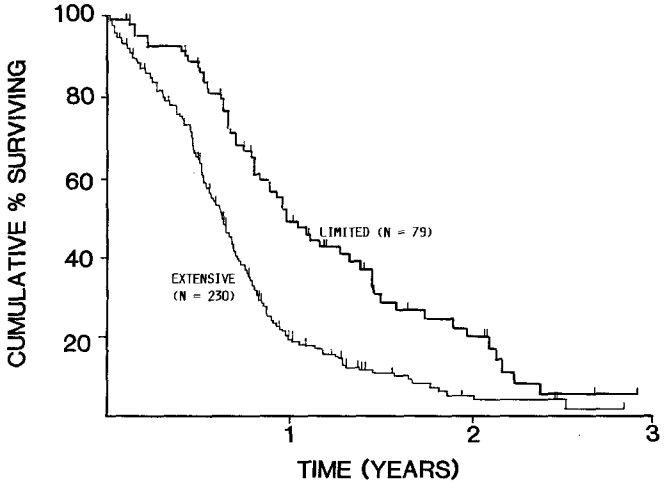

Fig. 1. Overall survival of 309 patients, comparing limited disease with extensive disease categories ($P<0.00001$, log-rank test)

Table 1. Response to treatment in total of 275

	Limited	Extensive
	64 (23%)	211 (77%)
Complete responses 48 (17%)	8 (12%)	40 (19%)
Good responses 72 (26%)	31 (48%)	41 (19%)
Partial responses 32 (12%)	3 (5%)	29 (14%)

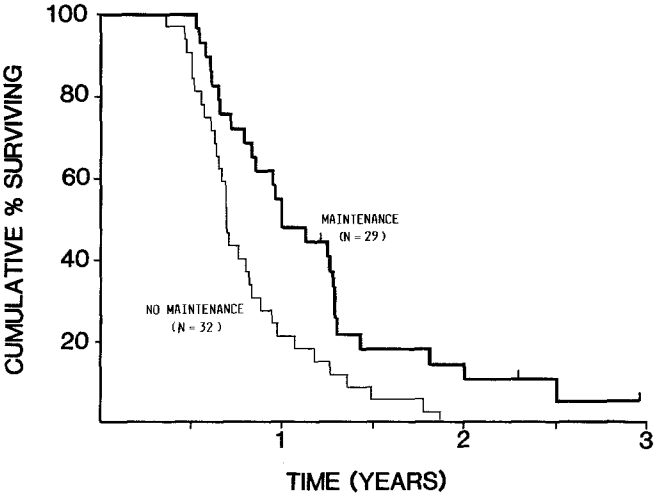

Fig. 2. Randomised extensive stage patients. Survival from start of treatment of maintenance versus no maintenance chemotherapy groups ($P=0.006$, log-rank test)

Table 2. Characteristics of randomised extensive stage patients

	Maintenance (29)		No maintenance (32)	
	N	%	*N*	%
Performance status				
Pretreatment				
WHO[a] 0–1	21	72.4	20	62.5
2–3	8	27.6	11	34.4
Not recorded			1	3.1
At randomisation				
WHO 0	16	55.2	12	37.5
1	10	34.5	15	46.9
2	0	0	1	3.1
Not recorded	3	10.3	4	12.5
Response to induction				
GR	10	34.5	20	62.5
CR	19	65.5	12	37.5
Age				
Median		62		59
Mean		60		59
Range		44–70		35–70

[a] WHO Performance Status Scale:
0, Able to carry out all normal activity without restriction
1, Restricted in physically strenuous activity, but ambulatory and able to carry out light work
2, Ambulatory and capable of all self-care, but unable to work; up and about more that 50% of waking hours
3, Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

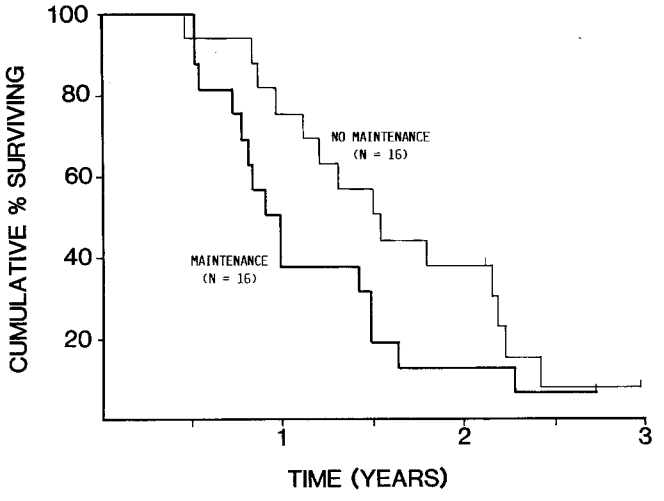

Fig. 3. Randomised limited stage patients. Survival from start of treatment of maintenance versus no maintenance chemotherapy groups ($P=0.13$ log-rank test)

allowing for pretreatment and randomisation performance status and for randomisation itself.

The equivalent curves for 32 randomised LD patients appear in Fig. 3. There is a nonsignificant trend in favour of no maintenance therapy. However, there were 5 early, isolated CNS relapses (4 brain, 1 cord) in the M arm and only 2 late, isolated CNS relapses (1 brain, 1 cord) in the NM group. On the grounds that maintenance chemotherapy would not be expected to prevent or delay isolated

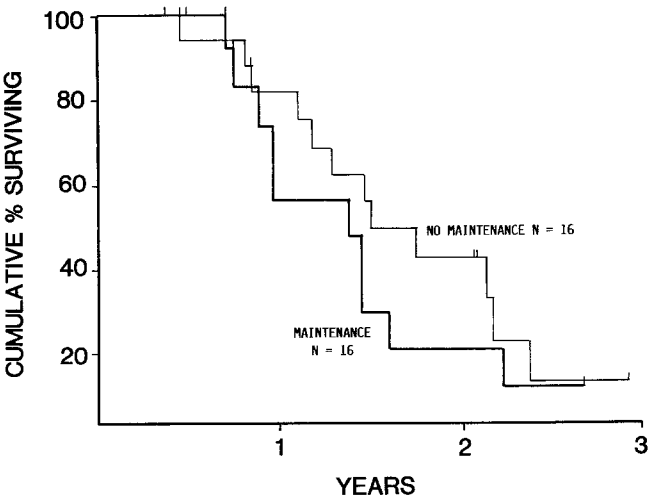

Fig. 4. Randomised limited stage patients. Survival from start of treatment of maintenance versus no maintenance groups, censored for isolated CNS relapses ($P=0.38$ log-rank test)

CNS relapse in ASCB, the data have been reanalysed in Fig. 4, with these 7 cases censored at the time of CNS relapse. There is no longer any suggestion of a trend.

The doses used for maintenance were lower than the induction doses (except in patients over 65), and the toxicity of maintenance was acceptable for most patients. However, 4 patients receiving maintenance therapy were withdrawn: 2 refused further treatment and 2 were withdrawn by their clinician because of toxic effects. In addition, doxorubicin was omitted from maintenance in 2 patients due to cardiotoxicity, and vincristine was omitted in 6 patients experiencing neurotoxicity. No randomised patients were excluded from analysis.

Discussion

Following chemotherapy, 60%–80% of patients with ASCB can expect symptomatic improvement, about half of these achieving complete remission [4]. The response in this study is comparable to those in other large reported series. Two other randomised trials have studied the duration of treatment. The CALGB [8] study is complicated by the inclusion of three separate randomisations within a single trial (combination versus single-agent chemotherapy; prophylactic cranial irradiation (PCI) versus no PCI; and maintenance versus no maintenance chemotherapy). After 28 weeks of therapy, patients with CR were randomised to no further treatment or to monthly maintenance treatment until relapse. Only 11 ED patients were randomised, allowing no conclusions in this group. The randomised LD patients had significantly longer survival with maintenance chemotherapy, than with no maintenance, but the duration of remission was no different. In contrast, the trial of Woods et al [10], published in abstract, showed no benefit for maintenance chemotherapy in 70 patients. The principal difference between these two trials is that the former continued with drugs that had been used to induce remission and thus were known to be active in the randomised patients (as in the present trial). In Woods' trial, on the other hand, after achievement of response the therapy continued with drugs that had not been used during induc-

tion. This may go some way towards explaining the different results. The theoretical attraction of using an alternative combination is the desire to suppress or delay the emergence of cells that are resistant to the first-line therapy. However, bringing in alternative combinations early on has not to date, improved overall results [1]. Woods' trial included 37 partial, as well as 33 complete remitters (all stages) in the randomisation. This may also contribute to the conflicting result. The inclusion of a majority of patients with only moderate chemosensitivity may have reduced the chance of demonstrating benefit from maintenance treatment.

In our study the small numbers of randomised LD patients, plus the presumably chance occurrence of excess isolated CNS relapses in the maintenance arm, precludes any conclusions in the LD trial. It is disappointing that 5 of these 7 relapses occurred in the brain in patients who had been irradiated. The very early appearance of these relapses probably signifies that CNS deposits were well established at the time of PCI.

In ED our results show benefit from maintenance chemotherapy, with a shift of the survival curve to the right, but no effect on long-term survival. Although the toxicity of maintenance chemotherapy was generally mild, the unquantifiable inconvenience, unpleasantness and fear associated with regular IV chemotherapy were considerable. Since this continued for 1 year or until relapse, most patients with ED were having treatment continuously until shortly before death.

Maintenance chemotherapy has been shown to confer no benefit in some other chemosensitive tumours (e.g. testicular teratoma; Hodgkin's disease). These differ from small cell cancer in that the majority of patients entering trials of maintenance therapy in these diseases have no residual disease and therefore cannot benefit from further treatment. In extensive small cell cancer patients achieving remission do have residual disease, which will recur and cause the patients' death. Our results suggest that continuing with the remission-inducing agents can prolong survival in patients with ED. Individual patients and their doctors may differ in their views as to whether the quality and duration of the added survival is worth the extra treatment. The greater need is for more effective remission induction in small cell cancer.

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