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Cyclic Alternating Polychemotherapy With or Without Upper and Lower Half-Body Irradiation in Small Cell Anaplastic Lung Cancer. A Randomized Study

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Abstract—*Ninety-six patients with small cell anaplastic lung carcinoma were given monthly chemotherapy with vincristine–doxorubicin–cyclophosphamide alternating with CCNU–methotrexate–etoposide for* 18 *months or until evidence of progressive disease. Forty-four patients were randomized to chemotherapy alone and* 52 *patients to chemotherapy plus* 600 *cGy of both upper and lower half-body irradiation given day* 60 *and* 100, *respectively.*

In 78 *evaluable patients surviving more than* 100 *days the overall response rate was identical in the two arms of the study,* 68% *vs.* 66%. *However, time to progression was significantly shorter in the irradiated patients* (P = 0.05). *Only* 25% *of the irradiated patients tolerated* ≥ 75% *of the scheduled dose of chemotherapy, against* 91% *of the non-irradiated patients* (P = 0.0001). *Thus, half-body irradiation was associated with a shorter time to progression and a decreased ability to give maintenance chemotherapy at proposed doses.*

INTRODUCTION

IN UNSELECTED patients with small cell anaplastic lung cancer (SMAC) median survival is approx. 12 months with current polychemotherapy regimens [1], and the addition of radiotherapy (RT) to the primary tumor with or without prophylactic cranial irradiation has not improved median survival significantly [2]. New principles of treatment are, therefore, of considerable interest. In 1980 Urtasun *et al.* reported a randomized study in which upper half-body irradiation (HBI) to a dose of 800 cGy in one sitting, followed by lower HBI to a similar dose 6 weeks later, resulted in the same duration of survival as polychemotherapy with CCNU, methotrexate and cyclophosphamide.

Based on the hypothesis that a combination of polychemotherapy with upper and lower HBI might improve survival in SMAC, we studied this combination in a randomized comparison against the same chemotherapy (CT) regimen alone. Since the use of cyclic alternating non-crossresistant CT regimens may result in a therapeutic benefit [4], two 3-drug regimens were selected, one of which was given intravenously while the other was given orally in order to simplify treatment.

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MATERIALS AND METHODS

Patients

Patients were eligible for the study if they had histologically-verified SMAC (WHO II, [1–4]), if they were less than 70-years-old, if they had a WHO performance score of 0–2, and if they had no clinical signs of CNS metastases. Patients with preceding thoracotomy with or without "radical" resection were allowed into the study.

Staging included clinical examination, chest X-ray, bone marrow aspiration and biopsy, bone scan, and a battery of liver function tests. Limited disease was defined as disease limited to one lung with or without involvement of mediastinal and/or supraclavicular lymph nodes. Extensive disease was characterized by the demonstration of metastases to soft tissue, bone or viscera, including CNS and malignant pleural effusion. Hepatic metastases were presumed in the presence of obvious hepatomegaly which could not be accounted for in any other way, or if at least two of the following three tests were abnormal: alkaline phosphatase ≥ 300 U/l, glutamic oxalacetic transaminase

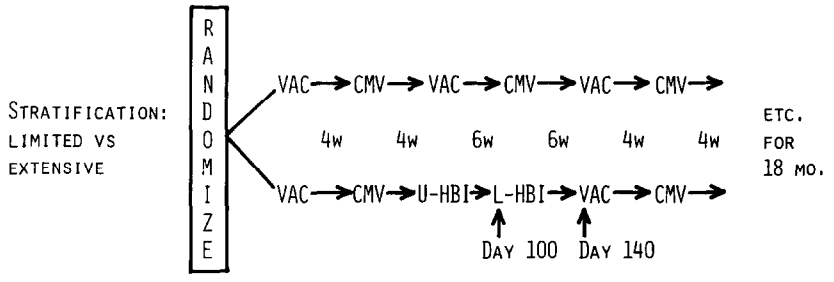

Fig. 1. Treatment plan. VAC = vincristine–doxorubicin–cyclophosphamide. CMV = CCNU–methotrexate–etoposide. U-HBI- = upper half-body irradiation. L-HBI = lower half-body irradiation. w = weeks.

$\geq$ 80 U/l, and gamma glutamylic transferase $\geq$ 30 U/l.

Treatments

Both upper and lower HBI were given with 8 Mev photons from a linear accelerator to a mid-line dose of 600 cGy in one sitting, using parallel opposing fields without shields, a source-to-axis distance of 200 cm and a dose rate of 70 rad/min. The upper and lower fields met at the level of the phrenicocostal sinus (top of L 1) and covered the entire body except the forearms and the lower legs. Radiation nausea was minimized using a 24-hr pretreatment programme of hydration, corticosteroids and anti-emetics, as described by Salazar *et al.* [5]. During both upper and lower HBI patients were hospitalized for 48 hr.

The intravenous three-drug regimen, VAC, included vincristine 2 mg day 1, doxorubicin 50 mg/m^2 day 1, and cyclophosphamide 600 mg/m^2 day 1. The oral three-drug regimen, CMV, included CCNU 60 mg/m^2 day 1, methotrexate 20 mg/m^2 days 1 and 3, and etoposide 100 mg/m^2 day 1 through 4. Doses of 100% were given if leucocytes were $\geq$ 4000/μl and/or platelets $\geq$ 100000/μl and/or platelets between 99999 and 75000/μl. Below this level CT was withheld until cell counts recovered. In the majority of cases CT was given on an out-patient basis.

Treatment plan

Informed consent to participate in the study was required from all patients prior to randomization. After stratification according to limited or extensive disease patients were randomized (block randomization, closed envelope system) to receive VAC and CMV alternating for 18 months, or to the same CT with courses 3 and 4 substituted by upper and lower HBI, respectively (Fig. 1). The interval between courses was 4 weeks. However, between courses 3–4 and 4–5 the interval was 6 weeks in order to synchronize the CT arm with the RT arm, in which each HBI necessitated a 6-week rest to allow the bone marrow to recover. In order to receive both radiation treatments a patient had to survive for at least 100 days, and to receive the first course of CT after both HBI treatments a patients had to survive for at least 140 days.

Evaluations

Complete response (CR) was defined as total disappearance of all disease manifestations, while partial remission (PR) was defined as more than 50% reduction in the products of the largest perpendicular diameters of the chosen indicator lesion. To qualify as a CR or PR a response was to last for at least 90 days from the onset of treatment. Responses of less than 90 days were classified as no change (NC), as were responses involving less than 50% tumor regression lasting more than 90 days. Progressive disease (PD) was defined as more than 25% tumor increase in spite of treatment, or a NC of less than 90 days. Patients with "radical" resections were classified as CR if new lesions did not appear within 90 days from the onset of protocol treatment.

For CR, PR and NC response duration was calculated from the first day of treatment, and survival was also calculated from the first day of treatment. All deaths were considered to be due to SMAC. Treatment after PD might include local palliative RT and/or prednisolone, but not additional CT.

Curves depicting time to progression and survival were obtained by the methods of Kaplan and Meier, while Gehan's test was employed to establish whether statistically signifiant differences between the two treatment groups existed. Follow-up was complete with only 3 patients still alive (at 503, 566 and 1432 days) at the time of analysis. All cases were reviewed independently by two observers (HB and PVH).

RESULTS

From March 1981, through January 1984, 96 eligible patients were randomized. A total study population of 150 patients was aimed at, but following an interim analysis in January 1984, show-

Table 1. Results of randomization

	Evaluable, survived > 100 days		Not-evaluable, survived < 100 days	
Treatment	CT	CT + HBI	CT	CT + HBI
Number of patients	37	41	7	11
Median age (range)	63 (46–69)	60 (42–69)	62 (50–66)	65 (51–68)
Males/females	27/10	30/11	7/0	6/5
Limited/extensive	23/14	25/16	3/4	2/9
WHO performance				
score 0	9	14	1	0
score 1	21	21	3	9
score 2	7	6	3	2

CT = chemotherapy. HBI = half-body radiation.

Table 2. Response data, evaluable patients

Treatment	CT				CT + HBI			
Stage of disease	Limited		Extensive		Limited		Extensive	
"Radical" resection	5		1		3		1	
Complete remission	6	74%	0	57%	4	72%	1	56%
Partial remission	6		7		11		7	
No change	4		4		4		4	
Progressive disease	2		2		3		3	
Subtotal	23		14		25		16	
Total	37				41			

CT = chemotherapy. HBI = half-body irradiation.

ing that time to progression was significantly shorter in the irradiated patients, the trial was stopped.

In order to make a comparison between the two arms of the study meaningful, it was necessary to consider all patients who did not survive 100 days as not evaluable. Patients who did not reach this landmark could not have received both HBI treatments, and accordingly analysis of patients surviving less than 100 days would involve comparisons of cases having had more or less the same treatment. Table 1 shows the results of the randomization. By chance more patients with extensive disease had been randomized into the CT plus HBI arm when the trial was stopped (25 vs. 18 patients). However, more patients with extensive disease survived less than 100 days in the CT + HBI arm. Consequently, the randomization procedure divided the 78 evaluable patients who survived more than 100 days into two well-balanced groups. In the following analysis only the latter 78 patients will be considered.

Table 2 shows the response data for all evaluable patients. The overall response rate ("radical" resection + CR + PR) was 25/37, or 68%, in the CT arm, vs. 27/41, or 66% in the CT + HBI arm. When patients with limited and extensive disease were considered individually, there was also no difference between the two arms. However, 18 of the 19 patients achieving a CR or PR with CT had attained maximum response within 2 months against 14 of the 23 patients achieving a CR or PR with CT + HBI ($P = 0.023$). This indicates that HBI treatment may have provided some additional tumor shrinkage after the two first series of CT.

Figure 2 shows time to progression and total survival for all evaluable patients. Median time to progression was only 7 months in the CT + HBI arm against 9.5 months in the CT arm ($P = 0.05$). This was reflected in a median total survival of 9 months for CT + HBI patients vs. 11.5 months for CT patients ($P = 0.06$). In patients with limited disease (Fig. 3) median time to progression was 8.5 and 10.5 months, respectively, again with a significant shortening of time to progression in the CT + HBI patients ($P = 0.05$). As for median survival, the trend is also in favor of CT alone, 13.5 vs. 9.5 months, but this difference did not reach statistical significance ($P = 0.09$). In patients with extensive disease (Fig. 4) there were no significant differences between median time to progression, 8.5 vs. 7 months, or median survival, 10 months vs. 7 months. It seems, therefore, that

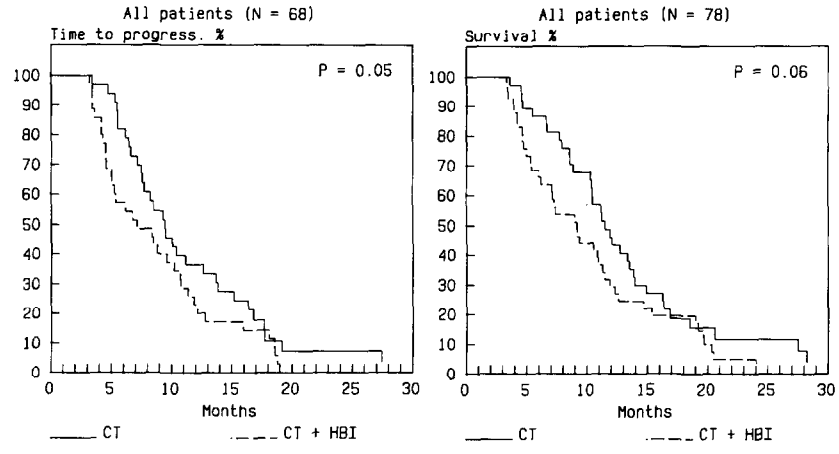

Fig. 2. Time to progression and survival for all evaluable patients. CT = chemotherapy. HBI = half-body irradiation.

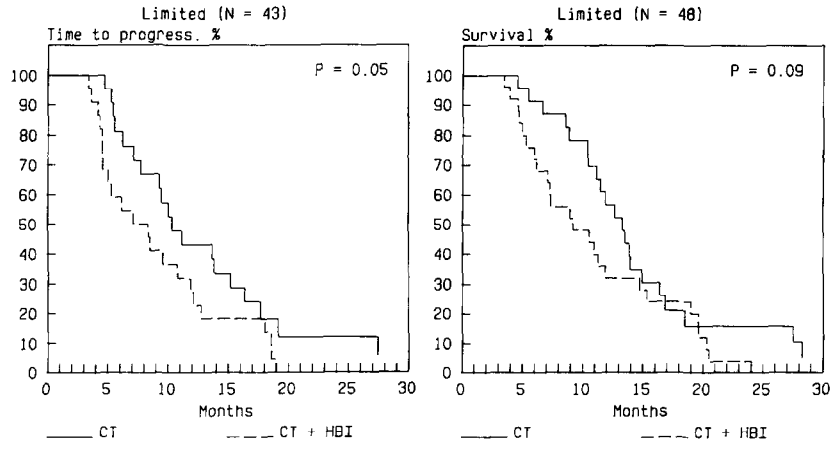

Fig. 3. Time to progression and survival for all evaluable patients with limited disease. Abbreviations as on Fig. 2.

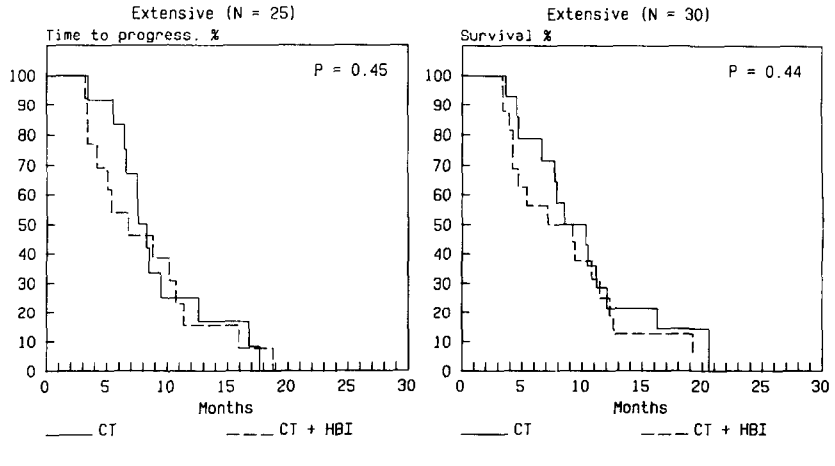

Fig. 4. Time to progression and survival for all evaluable patients with extensive disease. Abbreviations as on Fig. 2.

Table 3. Disease progression before day 140

	CT	CT + HBI	
PD before day 90	4	6	
PD & NC progressing after day 90 and before day 140	1	7	$P = 0.2$
Total	5	13	

CT = chemotherapy. HBI = half body irradiation. PD = progressive disease. NC = no change.

Table 4. Tolerance to chemotherapy after day 140

	CT	CT + HBI	
Progression before day 140	5	13	
Chemotherapy after day 140	32	28	
tolerated 75–100% dose	29 (91%)	7 (25%)	
tolerated 50–75% dose	3 (9%)	17 (61%)	$P < 0.0001$
tolerated < 50% dose		4 (14%)	

CT = chemotherapy. HBI = half-body irradiation.

HBI was associated with a shorter time to progression primarily in patients with limited disease. For the sake of completeness, survival data were also analyzed including the 18 not-evaluable patients. This did not result in any essential changes of the survival curves (not shown).

Since HBI was given after only two courses of CT, the number of residual tumor cells might be large enough to carry an increased risk of relapse in the irradiated patients during the period without CT. The number of patients with disease progression before 90 days was comparable in the two arms. However, the number of patients showing progressive disease between day 90 and day 140—that is, during the period of CT rest following HBI—appears to be increased in the RT arm, although this difference is not statistically significant due to the small figures (Table 3).

HBI produces bone marrow depression which recovers fairly well in 6 weeks [5]. Nevertheless, one might expect patients with prior HBI to show decreased tolerance to subsequent CT. Table 4 shows that this expectation was borne out. Only 25% of the irradiated patients tolerated 75% or more of the scheduled dose of CT, against 91% of the non-irradiated patients. This difference is highly significant. The reduced tolerance to CT of the irradiated patients manifested itself especially through a marked tendency to anemia and thrombocytopenia, while leucopenia was less of a problem (Fig. 5).

No cases of radiation pneumonitis or congestive heart failure were observed. As regards other toxicities, e.g. nausea, neuropathy, cystitis, stomatitis, febrile episodes and alopecia, there were no significant differences between the two treatment groups.

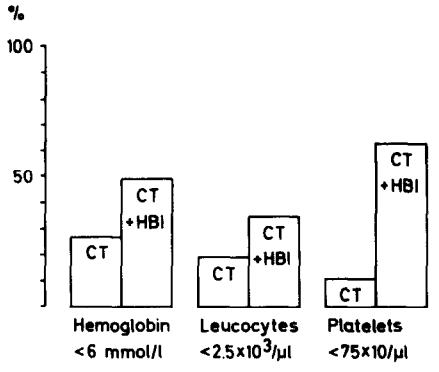

Fig. 5. Hematologic toxicity. Percentage of patients with hemoglobin <6 mmol/l, leucocytes <2.5 × 10^3/µl and platelets <75 × 10^3/µl. Abbreviations as on Fig. 2.

Since the HBI covered the entire CNS, a prophylactic effect against CNS metastases was anticipated in the irradiated patients. However, the number of patients showing clinical signs of this complication was two in the CT + HBI arm and three in the CT arm, and thus no difference was apparent. Overall, surprisingly few patients showed clinical signs of CNS metastases, but systematic screening using brain isotope scans or CT scans was not performed.

DISCUSSION

HBI has been used in SMAC with or without local tumor irradiation and with or without concomitant CT. In one pilot study of 19 patients with extensive disease 600 cGy of upper HBI was combined with 2000 cGy of local chest irradiation and 2-drug CT. Median survival of all patients treated was about 7.5 months (our estimate). These results were felt to be "encouraging" [6]. A very similar pilot study using 3-drug CT in addition to 600 cGy of upper HBI and 2000 cGy of local chest irradiation yielded a median survival of 9 months in 12 patients (4 extensive, 8 limited disease). These results were thought to be "disappointing" [7]. A third phase-2 study of 24 patients with limited disease combined 600 cGy of both upper and lower HBI with 2000 cGy of local chest and cranial irradiation plus 3-drug CT. Median time to progression was 9.9 months, and median survival was 14 months. The combined treatment was characterized as "efficacious" [8]. In a phase-3 study 29 "poor-prognosis" patients received 2 courses of 3-drug CT and were then randomized to 10 further courses of the same CT or to 700 cGy of both upper and lower HBI. Median survival was 7 months with HBI and 8

months with CT. It was concluded that HBI might achieve a similar palliative result as CT with much less subjective toxicity [9].

In the largest phase-3 study of HBI in SMAC published so far, 64 patients (36 limited, 28 extensive disease) were randomized to 800 cGy of upper and lower HBI or 3-drug CT, following 4000 cGy of initial local chest irradiation. Median survival for all stages combined was 10 months for CT and 5 months for HBI. In patients with limited disease the two treatments both resulted in a duration of survival of 10 months, but in patients with extensive disease CT was significantly superior (10 vs. 3.5 months) to HBI [10].

When comparing the results of these five studies with the results of studies in which CT was used alone or with local chest irradiation [11–13] nothing indicates any real benefit from the use of HBI. The results of the present study are in keeping with this view, since HBI was clearly associated with a shorter time to progression and a decreased ability to give maintenance CT at proposed doses. Even though there were indications that HBI provided additional tumor shrinkage in 9 of 23 patients after the two first series of CT this did not result in any prolongation of time to progression or survival. The reason for the absence of clinically significant benefit of HBI may be uncontrolled tumor growth during the CT rest period necessitated by the HBI, as well as decreased tolerance to CT following HBI (Tables 3 and 4). The separation of the HBI fields in the present study was located somewhat higher than in previous trials using the iliac crest [5] or umbilicus [10] as dividing line. Therefore, radiotherapy of the lower third of the liver was delayed 6 weeks. Further, a minor part of the bone marrow, corresponding to L 1–4, had a shorter rest period before resumption of CT than in other trials. Whether these factors may have contributed materially to worsen the prognosis of the HBI patients cannot be assessed.

The available studies of HBI in combination with CT have as a common factor the placing of HBI quite early in the treatment sequence, typically after two courses of induction CT ([6–9], present study). In theory, HBI might still be beneficial as a "late intensification" treatment after the termination of CT, if HBI produces a 1–3 log cell-kill as has been estimated [5]. It has been shown recently in two randomized studies that no significant survival advantage is conferred by the continuation of CT beyond 6 months [14, 15]. Accordingly, HBI might be given as "late intensification" treatment at this time in responding patients. This strategy was employed in a phase-2 study in which 6 courses of 3-drug CT was followed by 2500 cGy of local chest irradiation and 300–600 cGy of upper HBI in 85 patients with extensive disease [16]. Median survival was 8 months and again, no better than with CT alone [1, 11–13].

In conclusion, at this point the available data do not support the hypothesis that the addition of HBI to CT improves treatment results in SMAC over than seen with CT alone.

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