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Cisplatinum and Bleomycin for advanced or recurrent squamous cell carcinoma of the head and neck: a randomised factorial phase III controlled trial*

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Summary. A phase III 2×2 factorial trial of cisplatinum and bleomycin in 116 patients with recurrent or advanced squamous cell carcinoma of the head and neck is reported.

Thirty percent of patients proved to be unfit for chemotherapy, and of those treated progression of tumour was the commonest "response". However, 25% of patients achieved a partial or complete response, with no significant difference in response rates between the treated arms.

The median number of courses received was 1 (range 0–6) and the commonest causes for discontinuation of treatment were renal toxicity and death.

Bleomycin reduced survival, but not significantly so, whereas cisplatinum prolonged median survival significantly by 10 weeks.

Significant predictors of survival, in addition to treatment by cisplatinum, were age, performance status, N status, number of courses and response of the tumor.

Introduction

Chemotherapy can be used in the treatment of squamous carcinoma of the head and neck, first as an adjuvant to radiotheraphy or surgery, or secondly for palliation in patients with recurrent or advanced disease unsuitable for radical treatment. Many phase II trials have been reported which show that three agents are active: cisplatinum, methotrexate , and bleomycin. However, very few phase III trials of palliative or adjuvant therapies treatment have been carried out.

Sadly, adjuvant trials need about 800 pantients (necessitating a multi-centre study) and 5 – 10 years to complete. Moreover, adjuvant chemotherapy raises ethical difficulties because chemotherapy could kill some patients who would have been cured by established methods alone. Finally, the few phase III trials reported [2, 9, 12] have indicated that, at best, the adjuvant regimens tested so far do not improve survival rates.

A more helpful practical approach may therefore be to use phase III trials to assess those agents and combinations of agents which are thought to be active as palliative therapy. Such trials only require about 100 patients and can be completed in 1–2 years. Active regimens thus identified could be submitted later to trials as adjuvant therapy.

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Another issue to be resolved is whether treatment with several drugs is more effective than single-agent treatment [15]. The addition of methotrexate to cisplatinum merely increased toxicity, and not survival [3]. Phase II trials of a combination of cisplatinum and bleomycin have consistently shown a response rate (partial and complete) of about 50% [16].

We now report a factorial phase III trial of cisplatinum and bleomycin in the treatment of advanced or recurrent squamous carcinoma of the head and neck.

Patients

Patients with histologically proven advanced or recurrent squamous cell carcinoma of the head and neck unsuitable for surgery or radiotherapy were entered into the study. All patients seen between Januar 1982 and April 1984 with such tumours were admitted. The patients' characteristics are given in Table 1. After 95 patients had been entered, analysis showed that cisplatinum prolonged survial significantly, whereas bleomycin did not [II]. We therefore stopped recruitment to the control and bleomycin arms, but continued recruitment to the other two arms, in an attempt to assess whether there is synergism between cisplatinum and bleomycin. A further 25 patients were admitted, bringing the total to 120, but 4 patients were withdrawn because of protocol violations, leaving a final total of 116.

Informed consent. Ethical Committee approval was obtained for the study. The trial, its purpose, and the side effects of the drugs were discussed with each patient and his relatives.

Method

Pretreatment assessment included classification of each tumour by site and stage according to the UICC classification [17], assessment of the patients' general condition and Karnofsky performance status [4], a complete physical examination, routine haematological and biochemical screening, liver function tests, 24-h urinary creatinine clearance, serum albumin levels, chest X-ray, electrocardiogram, pulmonary function tests and audiometry. The UICC TNM classification referred to the *original* tumour and not to the stage of the tumour when it recurred. Patients originally treated elsewhere were staged T_xN_x.

Table 1. Patient's details

	Control group	Bleomycin alone	Cisplatinum alone	Cisplatinum + Bleomycin
Site				
Mouth	6	3	8	9
Oropharynx	6	5	5	4
Hypopharynx	6	5	10	9
Larynx	6	5	11	5
Other	2	4	4	4
Men	18	14	28	20
Age (mean)	66.0	61.4	61.4	64.6
Women	8	8	10	11
Age (mean)	61.8	61.8	65.6	60.3
Karnofsky				
Median	70	60	70	60
Range	30–80	30–80	20–90	20–90
Advanced tumours	4	9	12	11
Recurrent tumours	22	13	26	20
Site of recurrence				
Primary	7	5	10	6
Nodes	7	6	7	9
Metastases	1	1	2	2
Primary + nodes	5	0	4	2
Primary or nodes + Metastases	2	1	3	1
Time to recurrence (weeks)				
Median	53	46	60	47
Range	13–591	23–130	12–315	12–202

Dosage and administration. Prehydration with 1 litre of dextrose/saline over 6 h to establish a diuresis of 150 ml/h was followed by cisplatinum 100 mg/m^2 as a continuous infusion over 24 h. Those patients randomised to receive bleomycin were given a continuous infusion of 15 mg per day for 5 days (commencing on the 3rd day if they had also received cisplatinum). Chemotherapy was given at monthly intervals.

Assessment during the trial. During chemotherapy there were frequent checks for specific symptoms and for abnormalities of peripheral blood counts, urea and electrolytes, pulmonary and audiometric function.

Patients receiving cisplatinum had a 24 h urinary creatinine clearance performed before each cycle of chemotherapy. If the creatinine clearance was greater than 60 ml/min then the full dosage of cisplatinum was given. If the creatinine clearance was between 50 and 60 ml/min the dose was reduced to 50 mg/m^2. Patients with creatinine clearance below 50 ml/min were not given cisplatinum.

Treatment was not repeated unless the peripheral white cell and platelet counts were satisfactory.

Patients with a history of pulmonary disease or in whom a pulmonary diffusion defect either was present or developed (as shown by a low DCO or radiological evidence of pulmonary fibrosis) were not given bleomycin.

Cessation of treatment. Treatment was discontinued after (a) three treatment cycles with no evidence of objective response or (b) the development of major toxicity.

Assessment of response. A *partial* response was defined as a reduction of at least 50% in the product of two perpendicular diameters of all assessable lesions. A *complete* response was defined as the absence of clinically detectable disease [17].

Patients were seen at monthly intervals and the tumour was measured where possible, or x-ray images of pulmonary metastases for example, were measured. In many patients the tumour could be measured, for example in the pharyngeal or laryngeal lumen, and an attempt was made to assess the size of these tumours visually.

Statistical considerations

The median survival for this group of patients is 11 weeks, and the survival curve follows an exponential distribution [9]. A sample size of about 100 is needed to demonstrate a true prolongation of median survival by at least 12 weeks, with a type I error of 5% and a type II error of 20%. Patients were randomised to the four treatment groups by random number tables. Patients who proved to be unsuitable for, or who refused, treatment remained in the group to which they had been assigned for analysis.

Trial design. A 2 × 2 factorial design was used [7], that is patients were randomised to the following four arms:

(I) No treatment; (II) cisplatinum alone; (III) bleomycin alone; (IV) cisplatinum and bleomycin.

Survival was assessed by the actuarial method [1], and differences in survival were analysed by the log rank method [8].

Assessment of prognostic factors. Regression analysis was done using GLIM (Generalised Linear Interactive Modelling), taking into account whether the patient is alive or dead, and his period of survival. The following were the independent variables: age, sex, Karnofsky status, site of the primary tumour and its T and N status, site of recurrence (e.g., primary tumour, nodes etc.), treatment arm, number of courses and response.

Follow-up and storage of data. The patients were followed up personally and no patients have been lost to follow up. The data were stored and analysed on a CBM 8032 Microprocessor.

Results

Number of courses

The number of courses received by each group is shown in Table 2, and the survival related to number of courses, in Table 3. Of the 90 patients in the chemotherapy arms, 27 (30%) were unfit for chemotherapy: only 5 received more than three courses (it was originally intended that six should be given), and the median number of courses was one. Progressive nephrotoxicity and death were the commonest limiting factors.

The commonest contraindication for treatment was poor renal function (creatinine clearance < 50 ml/min).

Table 2. No of courses received

Number of courses	Bleomycin	Cisplatinum	Cisplatinum + Bleomycin
0	7	10	10
1	4	9	7
2	9	11	2
3	2	4	1
4	0	3	0
5	0	0	0
6	0	1	1

Table 3. Survival no. of courses, and Karnofsky status in all chemotherapy groups

No. of courses	No. of Patients	Median survival (days)	Karnofsky (median)
0	27	52	50
1	20	65	70
2	22	119	70
3+	12	350	70

Table 4. Response

	Bleomycin	Cisplatinum + Bleomycin	Cisplatinum
Progression of tumour	13	21	21
No response	6	8	6
Patrial response	3	7	3
Complete response	0	2	1

Response rates

Of 64 treated patients, 16 (25%) (95% confidence limit 10.6%) experienced a partial or complete response (Table 4), but progression of the tumour was much the commonest response. There was no significant difference in response rate in the various treated groups ($X^2_4 = 2.22$). Three patients who had a response were then able to undergo radical treatment with radiotherapy (1 patient) or surgery. The two who underwent radical surgery are alive and free of disease 1½ years later. The timing and duration of response are shown in Table 5.

Multivariate analysis was used to assess those factors which were significant predictors of response. The independent variables were: age, sex, Karnofsky status, site, T stage, N stage, chemotherapy agent used, previous treatment, site of recurrence and number of courses. Only the number of courses proved significant ($P < 0.01$).

The survival of control patients and that of treated nonresponders are shown in Fig. 1: the survival of responders was prolonged but the survival of the treated nonresponders was very close to that of the control group.

Survival

The survival curves for the four individual arms are shown in Fig. 2. The median prolongation of survival due to cisplatinum was 10 weeks. The survival curves of the two cisplatinum arms compared with the two non-cisplatinum arms are shown in Fig. 3, which is made possible by the factorial design of the trial. A similar curve for the bleomycin and non-bleomycin arms is shown in Fig. 4.

Table 5. Timing and duration of response

Arm	No. of courses to response	Duration of response (days)
Bleomycin	1, 2, 1	13, 14, 40
Cisplatinum	1, 1, 1, 1, 1, 2, 2, 1, 1	45[a], 46, 50, 103[a], 125, 183, 189, 242, 334
Cisplatinum + bleomycin	2, 1, 1, 1	49, 78, 295, 309

[a] These two patients underwent surgery at this point and are alive and free of disease at 681 and 513 days, respectively

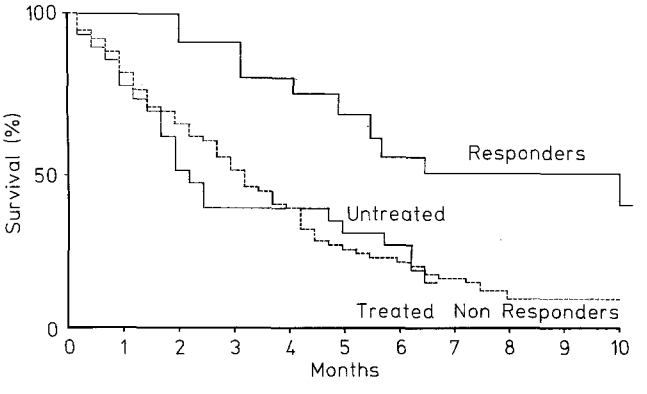

Fig. 1 Survival of responders, treated nonresponders and control patients

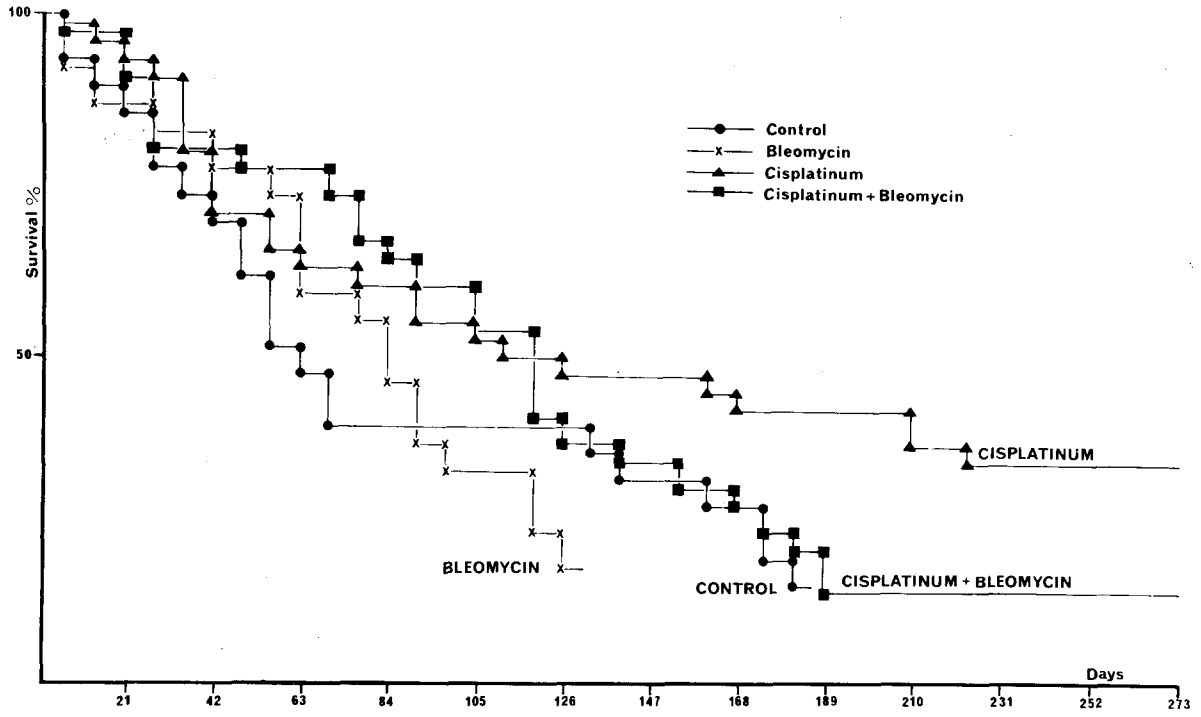

Fig. 2. Survial in four individual groups

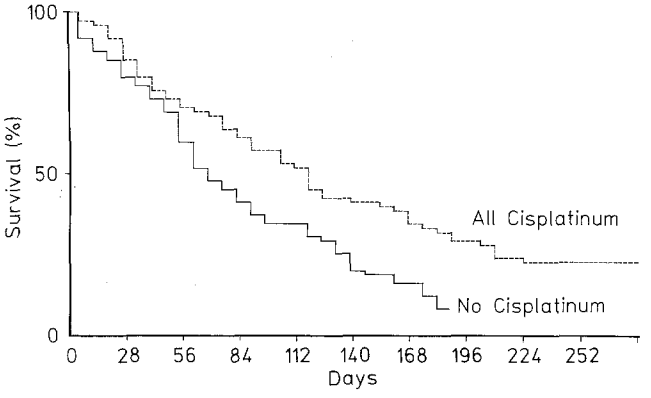

Fig. 3. Survival curve of the two cisplatinum arms compared with that of the two non-cisplatinum arms

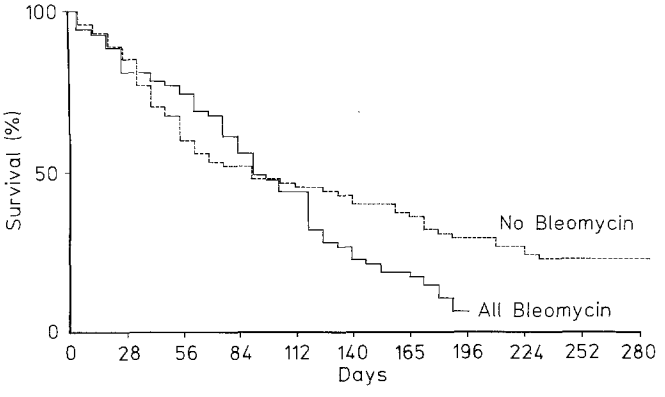

Fig. 4. Survial curve of the two bleomycin arms compared with that in the two non-bleomycin arms

Table 6. Log rank test

Comparison	$\times_1^2$	*P*
Bleomycin vs control	1.11	N.S.
Cisplatinum vs control	5.24	<0.05
Cisplatinum + Bleomycin vs. control	0.84	N.S.
Cisplatinum vs Cisplatinum + Bleomycin	3.18	N.S.
2 Cisplatinum arms vs 2 non Cisplatinum arms	9.09	<0.01
2 Bleomycin arms vs 2 non-Bleomycin arms	3.40	N.S.

The results for the log rank test for comparison of the above groups is shown in Table 6. The only significant prolongations of survival were for the groups receiving cisplatinum. As the curves for cisplatinum and cisplatinum plus bleomycin crossed the result of the log rank test was verified by a Kolmogorov–Smirnov test. This also gave a result which almost reached significance in favour of cisplatinum alone ($P=0.065$)

Prognostic factors

The results of regression analysis are shown in Table 7.

The significant predictors of survival were age, performance status, node status (N_3), treatment with cisplatinum, number of courses and response of the tumour. Age and node status were negative prognostic factors; that is to say, survival decreased with increasing age, and survival for N_3 patients was worse than that for patients with N_0, N_1, or N_2 disease. The remaining significant factors were

Table 7. Prognostic factors

Age	<0.02
Sex	N.S.
Karnofsky performance status	<0.01
Serum albumin	N.S.
Site of recurrence	N.S.
T status	N.S.
N status	
N_1	N.S.
N_2	N.S.
N_3	<0.001
Previous treatment	N.S.
Site of primary tumour	N.S.
Treatment	
Cisplatinum	<0.02
Bleomycin	N.S.
Cisplatinum + bleomycin	N.S.
Number of courses	
1	<0.001
2	N.S.
3	N.S.
4 +	N.S.
Response	
Partial	<0.01
Complete	<0.02

positive. The survival of all patients related to Karnofsky status is shown in Table 8.

The median survival of patients with a serum albumin of 36 g/100 ml or more was 114 days, whereas the survival for patients with serum albumin of 35 g/100 ml or less (the WHO definition of hypoalbuminaemia) was only 76 days. Despite this obvious difference the level of serum albumin, did not appear to be a significant prognostic factor on analysis by GLIM, but it appears that the reason for this was confounding by the performance status: there is a highly significant correlation between Karnofsky status and serum albumin ($r = 0.25$, $t = 2.80$, $P < 0.01$).

Toxicity

The change in creatinine clearance, haemoglobin and white cell count with number of courses is shown in Tables 9–11. Other forms of toxicity are shown in Tables 12 and 13. The grades used are those defined by Miller et al. [6].

Preteatment audiograms were done in all patients receiving cisplatinum. Ten patients who had pretreatment audiogram were unfit to attend for post-treatment audiograms. Sadly, a large number of the audiograms in the remaining patients were accidentally destroyed, and serial audiograms were preserved for only 18 patients. The results are shown in Fig. 5.

Table 8. Effect of Karnofsky status on survival

Status	Median survival (days)
80 + 90	130
60 + 70	110
40 + 50	71
< 40	7

Table 9. Creatinine clearance ml/min

No. of courses	Mean	SD
0	74.3	27.4
1	63.9	29.5
2	57.8	28.9
3	65.4	16.4

Table 10. Haemoglobin g/100 ml

No. of courses	Mean	SD
0	13.28	1.70
1	12.43	1.65
2	11.37	1.73
3	11.84	1.07

Table 11. Total white count 10^9/l

No. of courses	Mean	SD
0	9.66	3.14
1	8.17	3.76
2	8.16	3.51
3	6.89	1.48

Discussion

In brief, this trial showed that 30% of our patients with advanced/recurrent head and neck cancer were unfit for chemotherapy with cisplatinum or bleomycin, and that a further 20% only received one course. Proposals for cross-over designs are therefore largely irrelevant. Survival increased with increasing number of courses given.

The commonest 'response' was progression of the tumor, but 25% of patients experienced a partial or complete response; this is similar to response rates previously reported for these agents [14]. Three of four patients who responded did so after one course, and the rest after two courses. It seems pointless to continue beyond two courses if there is no response. If there is a partial response, however, chemotherapy should be continued: Two patients who showed an initial partial response went on to achieve a full response. The survival of treated nonresponders did not differ from that of controls; that is to say, the patients who do not respond do not appear to be made worse by chemotherpy.

Cisplatinum significantly prolonged survial, the prolongation of median survival being 10 weeks, that is survival time was doubled. Bleomycin shortened survival but not significantly so. There was no synergism between cisplatinum and bleomycin; indeed, in patients treated with the two agents together survival was very similar to that in control patients. Similar disappointing results with bleomycin in combination with vincristine and methotrexate have been reported by others [13].

Significant predictors of survival other than treatment with cisplatinum included age, performance status, node status, number of courses, and response, most of which are well-known predictors of survival [14].

Table 12. Nature and frequency of side effects encountered with each chemotherapy regimen

	No. of events				No. of patients
	1	2	3	4	
Nausea and vomiting					
Cisplatinum	7	10	23	1	20
Cisplatinum + bleomycin	6	6	19	1	19
Bleomycin	2	3	2	–	1
Diarrhoea					
Bleomycin	1	–	–	–	1
Oral					
Cisplatinum + bleomycin	1	1	–	–	1
Bleomycin	2	–	–	–	1
Pulmonary					
Bleomycin	–	–	–	1 (pulmonary fibrosis)	1
Fever					
Cisplatinum + bleomycin	–	1	–	–	1
Bleomycin	1	2	–	–	3
Allergy (facial oedema)					
Cisplatinum	2	–	–	–	2
Cisplatinum + bleomycin	1	–	–	–	1
Alopecia					
Cisplatinum	–	2	–	–	2
Cisplatinum + bleomycin	–	2	5	–	5
Bleomycin	4	–	–	–	4
Cardiac					
Cisplatinum	1	–	–	–	1
Cisplatinum + bleomycin	–	–	–	–	1
Neurological (peripheral) paraesthesia					
Cisplatinum	1	–	–	–	1
Neurological (central) confusional states					
Cisplatinum + bleomycin	3	–	–	–	3
Bleomycin	2	–	–	–	2
					In all 73 pts had 1 or more complications (toxic) from chemotherapy

Table 13. Nature and frequency of renal and haematological toxicity

	Toxicity	Number of patients
Renal		
	Creatinine clearance < 60 ml/min	24
	Acute tubular necrosis (reversible)	2
	Acute tubular necrosis (irreversible)	1
Haematological		
	Myelosuppression WBC nadir < 4000	4
	Haemoglobin nadir < 10	8

Cisplatinum proved to be moderately nephrotoxic, despite all precautions such as prehydration, and was the most important cause of unsuitability for treatment. The haemoglobin and white cell count also fell during treatment, but not to catastrophic levels. The other major side effect was nausea and vomiting, experienced by over 70% of patients treated with cisplatinum.

It is difficult to comment on the audiometric toxicity, because of the unfortunate destruction of the records. Figure 5 shows what can only be interpreted as random variation about zero.

It is noteworthy that the response rates were similar in the three treated arms, but the survival rates were very different. This paradox may be explained in part by the acknowledged inaccuracies in measurement of the tumor [17]. The difference between response rates and survival rates highlights the superiority of phase III over phase II trials. One reason for this superiority is that survival, the end point of a phase III trial, is known with absolute accuracy. Response, the criterion of a phase II trial, cannot be measured accurately and is subject to observer bias.

The results of this trial do not answer the question of palliation. We have previously shown that patients with

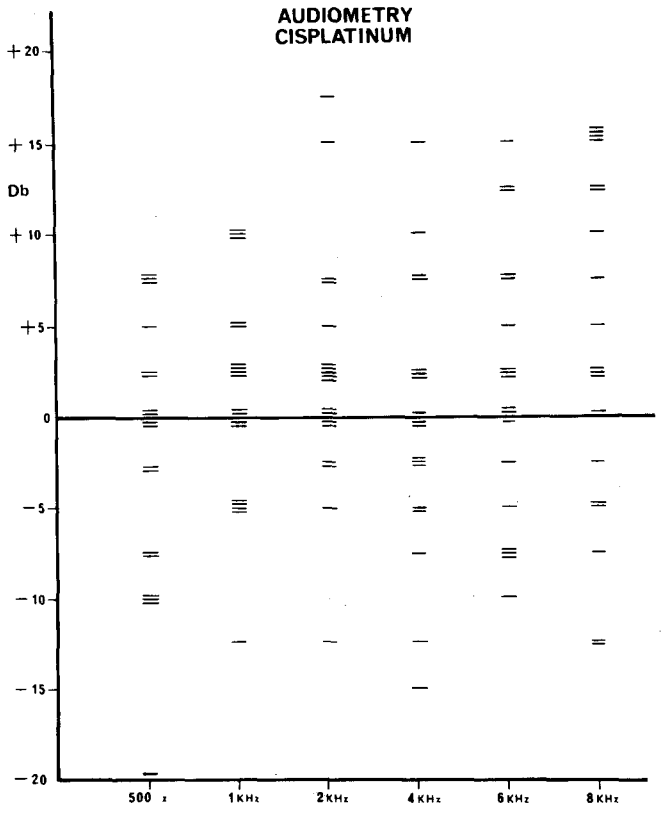

Fig. 5. Audiometric gain or loss after one course of treatment

longer survival spend longer periods at home [11]. We paid great attention in the design of the trial to attempts to measure the "quality of life", trying a pilot study using an analog scale, for example. In the event the matter proved exceedingly complex, but we are still trying to develop methods of assessing palliation.

The results of this trial must be regarded with caution. Trials with large numbers are required to allow for the wide individual variation in survival of these patients, which depents on factors as yet unidentified. Ideally, the trial should be repeated, but it is doubtful whether this is ethically justifiable.

Further questions generated by this trial include the following: (1), Is cisplatinum better than the previous 'standard' agent, i.e., methotrexate? (2) Can cisplatinum be combined effectively with other agents? It has recently been suggested that Cisplatinum + 5FU is an effective combination [5]. (3) What are the reasons why such a high proportion of these patients are unsuitable for chemotherapy? (4) How can palliation be measured?

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