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Treatment of head and neck cancer with CHART and nimorazole: phase II study

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Abstract

Background and purpose: Causes of failure of radiotherapy in squamous cell carcinoma of the head and neck probably include repopulation and hypoxia. Very accelerated schedules such as continuous hyperfractionated accelerated radiation therapy (CHART) overcome the repopulation problem but allow limited time for reoxygenation, so a hypoxic-cell sensitizer may be especially beneficial. Nimorazole is the only such agent to have shown a significant effect in a randomized controlled trial in head and neck cancer. Accordingly we studied the combination of CHART and nimorazole.

Methods: Sixty-one patients with advanced stage III (21) or IV (40) squamous cell carcinoma of the head and neck unsuitable for surgery were treated in a phase II study of the combination. The radiation dose was 56.75 Gy in 36 fractions in 12 consecutive days. Nimorazole was administered orally or enterally 90 min before radiotherapy at a dose of 1.2, 0.9, and 0.6 g/m^2 with the first, second and third daily fractions, respectively. This dosage consistently yielded plasma concentrations above 30 μg/ml.

Results: All the patients have been followed for a minimum of 2 years since treatment. Loco-regional control at 2 years is 55%, stage III 62% and stage IV 50%. Normal tissue effects were the same as those previously seen with CHART, except for a possible slight increase in acute skin reaction. Nimorazole toxicity was somewhat greater than with once daily administration in previous studies. Grade 3 nausea or vomiting occurred in 22% of patients. Two patients developed grade 1 peripheral neuropathy, and one patient died during treatment of encephalopathy, which was probably an idiosyncratic reaction to the drug.

Conclusions: Local control rates are higher than those previously seen with CHART, suggesting a positive effect of nimorazole. Further studies of hypoxia-modifying agents with accelerated radiotherapy are warranted, and nimorazole is the simplest of these.

Keywords: Accelerated radiotherapy; Nimorazole; Head and neck cancer

1. Introduction

Hypoxia and repopulation are two factors contributing to radiotherapy failure that can potentially be overcome by modification of treatment. Repopulation may be overcome by accelerated fractionation. A number of trials have shown that shortening overall treatment time improves local control in head and neck cancer [6,10]. The shortest treatment time so far tested in a large trial is that of the continuous hyperfractionated accelerated radiation therapy (CHART) regimen [14]. In the Medical Research Council (MRC) trial of CHART, a total dose of 54 Gy in 36 fractions of 1.5 Gy given three per day 6 h apart over 12 consecutive days gave the same local control as 66 Gy in 2 Gy daily fractions, but with a significantly lower rate of late normal tissue effects, suggesting a modest improvement in therapeutic index [2]. One disadvantage of CHART may be that the very short treatment time gives limited opportunity for reoxygenation of tumour cells, so that hypoxia becomes an important factor reducing the efficacy of the regimen.

An overview of clinical trials of hypoxic modification in head and neck cancer demonstrated a significant effect on tumour control and survival [12]. In the Danish Head and Neck Cancer (DAHANCA) 5 trial the hypoxic-cell sensitizer nimorazole increased 10-year loco-regional control in pharyngeal and supra-glottic carcinoma from 33% to 49% compared with placebo, without enhancing normal tissue effects [11]. The one disadvantage of nimorazole is nausea and vomiting, which can lead to poor compliance during a protracted course of treatment.

We considered that if nimorazole were given with CHART compliance would be less of a problem, firstly

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because the patients would be in hospital for the duration of the radiotherapy and so nausea could be better controlled, and secondly because the drug would be taken for only 12 days. There appeared to be a rationale for giving nimorazole with CHART, so we investigated this combination.

A phase 1 dose-escalation study of nimorazole with CHART was undertaken and has been reported previously [1]. It proved possible to give nimorazole with each fraction of CHART, at dosages which yield a plasma concentration of the drug of $\geq$30 μg/ml, which is considered to be adequate for radiosensitization [11]. There was no drug toxicity other than nausea and occasionally vomiting; compliance was not a problem. Tumour response appeared promising and there was no increase in the severity of acute normal tissue effects compared with historical controls treated with CHART alone. Accordingly, a phase II non-randomized study was undertaken to determine the efficacy of the CHART/nimorazole regimen.

2. Materials and methods

2.1. Radiotherapy

The patients were treated using a 6 MV linear accelerator and beam direction shells. The gross tumour volume and electively irradiated nodal areas received 37.5 Gy at the ICRU reference point in 25 fractions of 1.5 Gy, three fractions per day 5.5–6 h apart. In clinically node-negative cases the first station nodal areas at risk were irradiated electively; in node-positive cases the whole neck was treated electively. The primary tumour and involved nodes were given a boost of 19.25 Gy in 11 fractions of 1.75 Gy, to a total of 56.75 Gy. This dose is 5% higher than that used in the MRC trial [2], but approximately equal to that given in the original pilot study of CHART, when 54 Gy was prescribed as a minimum tumour dose [15]. In most cases the large volume was treated by parallel-opposed lateral fields and included the spinal cord. The boost volumes were individually planned to include a 1 cm margin around the gross tumour volume as defined clinically and on CT scans. The boost volume avoided the spinal cord, which never received a total dose of more than 44 Gy. A 12 h inter-fraction interval was preferred for the large volume to allow for the possible slower recovery of sub-lethal damage in the spinal cord. Accordingly, the boost volume was treated as the midday fraction on all but the first treatment day.

2.2. Nimorazole

Nimorazole was supplied by Pharmacia-Upjohn as 500 mg scored tablets. The drug was given orally 90 min before irradiation. If the patient had a naso-gastric or gastrostomy feeding tube the tablets were crushed and administered via the tube. The administration of nimorazole was supervised by a nurse and recorded on the patient's drug chart. A dose of 1.2 g/m^2 was given with the morning fraction, 0.9 g/m^2 with the midday fraction and 0.6 g/m^2 with the evening fraction. Doses were rounded to the nearest multiple of 250 mg. In the phase I dose-escalation study this regimen had been shown to give a plasma concentration of nimorazole consistently at or above 30 μg/ml at the time of irradiation, which is considered to be an effective sensitizing level [11]. Plasma samples were taken immediately before irradiation from five patients in this study chosen at random. The mean plasma nimorazole concentration, measured by the method previously described [1], was 47.9 μg/ml (range 34.9–61.9 μg/ml).

2.3. Patients

The entry criteria were as follows:

Histologically confirmed squamous carcinoma of upper aero-digestive tract.
Stage III or stage IV without distant metastases.
Unsuitable for surgery but considered fit for radical radiotherapy.
WHO performance status $\leq$2.
No significant renal or hepatic impairment, i.e. blood urea and liver function tests within the normal range, except for an isolated rise in the gamma-GT level in a patient who is known to be a heavy drinker or has had a recent general anaesthetic.

Any patient considered for the study was seen in a joint clinic by a surgeon and radiation therapist. Minimum investigations were endoscopy, biopsy, chest X-ray, full blood count, serum electrolytes, blood urea, creatinine and liver function tests. All patients seen in the two participating centres during the period of the study who fulfilled the above criteria were offered entry to the study. Written informed consent was obtained from all patients. The study was approved by the local ethics committees of the two centres taking part.

2.4. Assessment and follow-up

Nimorazole toxicity was assessed daily during treatment, using the NCIC Common Toxicity Criteria 1991 for nausea and vomiting. Acute radiation effects were scored once weekly during radiotherapy and until they were healed. Subsequently the patients were seen monthly for 6 months and then 3-monthly for assessment of tumour status and late radiation effects. The recording system for both acute and late effects was identical to that used in the MRC CHART trial [2].

3. Results

Sixty-one patients entered the study between 1997 and 1999, 49 at the Royal Marsden Hospital and 12 at Chelten-

Table 1
Characteristics of patients admitted to the study

	n
Site	
Oropharynx	34
Hypopharynx	10
Larynx	11
Oral cavity	3
Nasal sinuses	3
Males	45
Females	16
Performance status	
0	42
1	9
2	10

ham General Hospital. The patient characteristics are shown in Table 1, and the staging in Table 2. The minimum follow-up period is 30 months. No patients were lost to follow-up.

Six patients failed to complete the planned treatment, five of whom were performance status 2: two died of chest infection, one died of a perforated gastric ulcer, one did not start treatment because of logistic problems, and one refused to continue after the first treatment day. The sixth was the case of encephalopathy described below. Results are presented on an 'intention to treat' basis, i.e. all 61 patients are included in the analysis.

3.1. Local control

The overall loco-regional control rate of primary tumours and lymph node metastases within the irradiated volume was calculated by the Kaplan–Meier method and is shown in Fig. 1. Twenty-six patients so far have had residual or recurrent disease within the irradiated volume, including those who failed to complete treatment; nine failures were at both the primary site and regional nodes, 15 at the primary site only, and two in nodes only. The 2-year loco-regional control is 55% for the whole group, 62% and 50% for stages III and IV, respectively. The loco-regional control in the largest site group, i.e. the oropharynx with 34 patients, is 53%. Local control of the primary lesions is 77% for T3 and 39% for T4. Regional lymph node control at 2 years in the node-positive patients is 59%. Salvage surgery was attempted in six patients, three of whom remain free of disease.

Table 2
Staging of patients admitted to the study according to the UICC TNM system 1997

	N0	N1	N2	N3	Total
T2	0	4	2	0	6
T3	14	4	6	2	26
T4	12	5	9	3	29
Total	26	13	17	5	61

3.2. Survival

Overall survival calculated by the actuarial method is also shown in Fig. 1. To date, 37 patients have died of their head and neck cancer. Three patients developed lymph node metastases outside the irradiated volume, and five developed distant metastases, all without evidence of local recurrence. Five died of intercurrent disease without evidence of recurrence, and one of a presumed treatment complication. The 2-year crude survival is 47.5% for the whole group, 53% for stage III and 45% for stage IV.

3.3. Toxicity – nimorazole

Nearly all patients experienced some degree of nausea from nimorazole. Grade 3 nausea occurred in 13 (22%) and grade 3 vomiting in three (5%) cases. Vomiting was well controlled by cyclizine or metoclopramide. Compliance was good: apart from the five patients mentioned above who failed to complete radiotherapy, only three patients failed to take all doses of nimorazole as prescribed. In general, patients with gastrostomy or naso-gastric feeding tubes had less nausea and vomiting than those taking the tablets orally. Two patients described a mild transient peripheral sensory neuropathy.

One patient died during treatment apparently from a reaction to nimorazole. He was a man aged 73 treated for a supra-glottic carcinoma, who had smoked 30 cigarettes daily until 2 years before his diagnosis, and had been a lifelong heavy drinker. He had been voluntarily restricting his alcohol intake to six pints of beer a week shortly before his tumour had been found, and denied any symptoms suggesting acute alcohol withdrawal. He drank no alcohol whilst in hospital receiving treatment. On the second treatment day, after his fourth dose of nimorazole, he had an episode of transient loss of consciousness lasting a few seconds followed by a short period of disorientation. He recovered completely: a full physical examination and electrocardiogram were normal, so the event was considered to be a vaso-vagal episode. His treatment continued uneventfully until the seventh day when he had a brief self-limiting episode of shaking of both hands and arms, throughout which he remained alert and orientated. There were no post-ictal features and examination revealed no neurological abnormality. The following day he had three similar episodes, each lasting no more than 2 min; he also developed postural hypotension and became mildly confused. He was started on carbamazepine and dexamethasone, but his condition progressively worsened. His speech became slurred and he was unsteady on his feet. An MRI brain scan demonstrated generalized mild atrophy in keeping with his age and alcohol intake but no evidence of focal lesions, haemorrhage or infarction. A sample of cerebrospinal fluid was normal; an electroencephalogram demonstrated a slow normal record. He was seen by a consultant neurologist who confirmed the diagnosis of acute encepha-

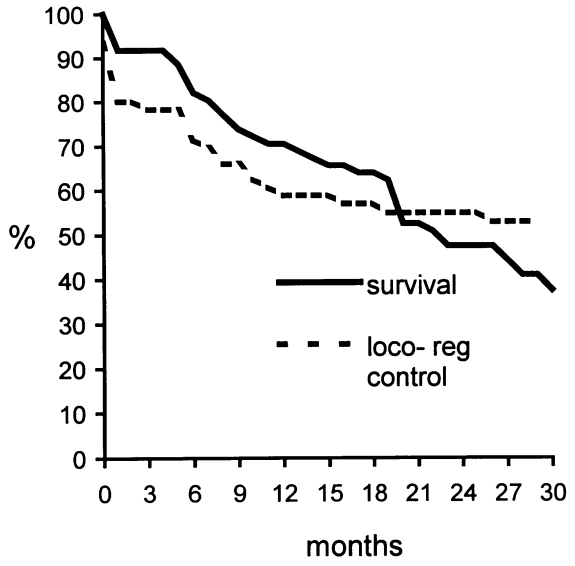

Fig. 1. Overall survival and loco-regional control of all patients in the study.

lopathy, so he was treated with vitamin B complex and diazepam, and his radiotherapy and nimorazole were stopped. At the time treatment was discontinued he had received 47.25 Gy in 30 fractions over 10 days, with nimorazole prior to each fraction. Despite all supportive measures his condition progressively deteriorated. He developed grand mal seizures, became comatose and died 10 days later. Autopsy showed an unsuspected second primary squamous cell carcinoma of the lung, bronchopneumonia, and centrilobular hepatic necrosis suggestive of a toxic aetiology. There was fibrosis and mucosal ulceration in the larynx but no evidence of viable tumour. An expert neuropathological examination of the brain reported multiple foci of necrosis in the cerebral and cerebellar white matter, with a predilection for long fibre tracts. In addition, bilateral symmetrical lesions indistinguishable from those found in Leigh's disease were present in hindbrain nuclei. As both metronidazole and misonidazole have been shown to produce Leigh-like lesions in rats, and high dose metronidazole can cause transient fitting or encephalopathy, the neuropathologist concluded that the changes seen were due to nimorazole CNS toxicity interfering with mitochondrial function leading to cellular energy deprivation.

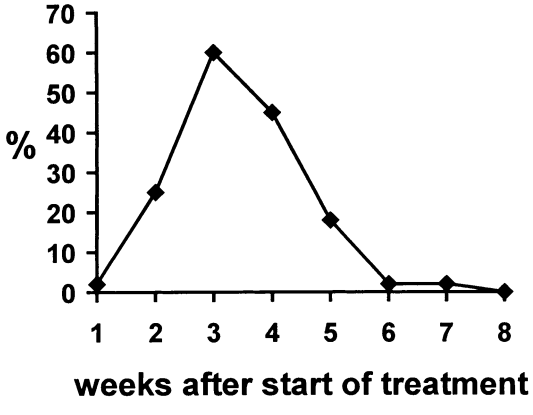

Fig. 2. Percentage of patients exhibiting grade 3 mucositis by weeks from start of radiotherapy.

3.4. Toxicity – radiation

All patients developed mucositis of at least grade 2 severity. The percentages of patients manifesting grade 3 mucositis plotted at weekly intervals after the start of radiotherapy are shown in Fig. 2. The time to complete healing of mucositis ranged from 5 to 11 weeks, with a median of 7 weeks. A total of 36 patients were tube-fed, either by a percutaneous gastrostomy or naso-gastric tube. In 22 the tube was inserted before radiotherapy, and in a further 15 during or after radiotherapy because of mucositis. In the two groups tube feeding continued after radiotherapy for a median time of 6 and 4 weeks, respectively. No patient lost more than 10% of body weight during and after treatment.

Dry desquamation of the skin was seen in 47% and moist desquamation covering more than 5% of the field areas in 15% of cases. Late radiation effects were mild. One patient developed osteoradionecrosis following tooth extraction, and one patient developed a small area of soft tissue necrosis following a check biopsy, which healed spontaneously. The actuarial incidence of late complication at 30 months is 5.4%.

4. Discussion

As a consequence of the results of the DAHANCA-5 study, nimorazole is now considered in Denmark to be a standard component of treatment for patients receiving radiotherapy for pharyngeal and supra-glottic carcinoma. A more recent study, DAHANCA-7 [10], compared a modestly accelerated regimen of 68 Gy in 2 Gy fractions given six times per week with the same dose given in five fractions per week, with both groups receiving nimorazole. Local control in the two arms of the trial was 68% and 56%, respectively ($P = 0.01$). The results in the six-fraction per week arm compare favourably with the more toxic chemoradiation schedules now used in many centres.

Despite the results of the DAHANCA studies, nimorazole has excited little interest outside Denmark. Many radiation oncologists are unwilling to accept that nimorazole has a significant sensitizing effect, because other radiosensitizers that are more active in vitro have failed to show a benefit – etanidazole for example [3,9]. However, nimorazole differs in important respects from the 2-nitro-imidazole compounds such as misonidazole and etanidazole. Its action has been shown to be independent of fraction size [13], and it has a less steep dose–response relationship compared with other sensitizers [16]. It is very soluble and therefore rapidly absorbed orally and diffuses readily into poorly-vascularized tumours: it is not lipophilic, therefore it has no cumu-

lative neurotoxicity and can safely be given with each fraction of a conventionally-fractionated course of radiotherapy. On the other hand, the dosage of the 2-nitro-imidazoles was limited by their neurotoxicity: in the etanidazole trials, for example, the drug was given with only half the course of radiotherapy [3,9].

Nimorazole has been used extensively in Denmark at a dose of 1.2 g/m^2 daily for 6–7 weeks, and no case of neurotoxicity has been observed. We observed two instances of very mild peripheral neuropathy similar to that sometimes seen after prolonged treatment with the closely related 5-nitro-imidazole compound metronidazole, and one case of encephalopathy. The dose intensity of nimorazole used in this study was higher than that in the Danish studies, which may account for neurotoxicity. In the patient who developed encephalopathy it seems unlikely that the previous heavy alcohol intake contributed, as there was no clinical or autopsy evidence of alcohol-related disease; in particular there was no cirrhosis: the mamillary bodies were normal and therefore there was no histological evidence of Wernicke's encephalopathy. Moreover, most of the patients in this study were heavy drinkers. As the symptoms appeared early in the course of treatment the encephalopathy may have been an idiosyncratic reaction to the drug.

Compliance with taking nimorazole was 95%, compared with 60% in the DAHANCA-5 study [11]. We attribute this to better control of nausea with the patients being in hospital throughout treatment, the use of enteral feeding for patients with swallowing difficulties, the short treatment time, and the fact that radiation mucositis with CHART does not occur until after the end of treatment.

Acute mucositis was similar in severity and duration to that seen in previous CHART studies [14]. Skin reactions with CHART are less than with conventional fractionation, but in this study a greater proportion of patients developed both dry and moist desquamation than in the CHART arm of the MRC trial, although still less than in the conventionally fractionated arm. A possible explanation is that the normal exposed skin of the head and neck, especially early in a course of radiotherapy, is relatively hypoxic. Late radiation effects were also similar to those seen in the MRC CHART study. Therefore, there was no suggestion that nimorazole increased normal tissue effects of radiotherapy when given by the CHART schedule, except possibly in the case of the skin.

The tumour control rates in this small group of patients compare favourably with those previously seen with CHART alone. The 2-year local control rates in the MRC trial [2], which excluded patients of performance status 2 and had a greater proportion of laryngeal cancers, were 40% for T3 and 31% for T4 tumours, compared with 77% and 39%, respectively, in this study. As a retrospective comparative group within one centre, 35 patients from the Royal Marsden Hospital who received CHART in the MRC study had 2-year local control rates of 44% for T3 and 27% for T4. The radiation doses in the MRC trial were approximately 5% lower than ours. However, a 5% increase in radiation dose would be expected to produce only a 5% improvement in tumour control [18], and would not therefore account for the differences. In comparison with the original pilot study at Mount Vernon Hospital, which used the same radiation doses as ourselves, our local control was similar for T4 but appreciably higher for T3 tumours. The apparently greater effect of nimorazole in T3 compared with T4 tumours may be merely a reflection of the small numbers treated, but a similar effect has been seen in hyperbaric oxygen trials [5]. It may be that hypoxia is less often the limiting factor in radiotherapy of very large tumours, or that hypoxia-modifying agents fail to penetrate them adequately.

There is therefore a suggestion from this study that nimorazole can improve the local control rate of CHART. Other studies combining a hypoxia-modifying agent with accelerated radiotherapy are also showing good results, such as the DAHANCA-7 trial mentioned above [10]. Initial studies with the nitrotriazole sensitizer senazole seem promising [7], as do those of carbogen and nicotinamde (ARCON) [8]. Results are similar to those of chemoradiation, now regarded in many quarters as standard treatment [17]. However, hypoxic-cell sensitizers do not enhance the action of radiation on normal tissues to the same extent as cytotoxic drugs [4]. There is a need for controlled trials comparing chemoradiation against accelerated radiotherapy plus hypoxia modification. Nimorazole is the simplest and cheapest method of hypoxia modification of proven efficacy so far.

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