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Conventional *vs* accelerated fractionation in head and neck cancer

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Summary From October 1990 to March 1994, 90 patients entered a prospectively randomised trial in head and neck cancer. All patients had verified squamous cell carcinoma and were referred for primary radiation therapy. Tumours originated in the oral cavity in 25, oropharynx in 37, larynx in 15 and hypopharynx in 13 cases. Patients' stages were predominantely T3 and T4 (71/90) and had lymph node metastases (60/90). Seventy-nine male patients and 11 female patients, with a median age of 57 years (range 37-76 years) were treated. Patients were randomised to one of three treatment options: conventional fractionation (CF) consisting of 70 Gy in 35 fractions over 7 weeks or continuous hyperfractionated accelerated radiation therapy (Vienna-CHART) or Vienna-CHART with administration of a single dose of mitomycin C on day 5 of treatment (V-CHART+MMC). By the accelerated regimen a total dose of 55.3 Gy was given in 33 fractions within 17 consecutive days. Acute mucositis was the main toxicity recorded in those patients treated by accelerated fractionation, although the overall duration of mucosal reaction did not differ in the three treatment groups. There was no influence on local toxicity if MMC was added to radiation therapy or not. Those patients treated with additional MMC experienced a grade III/IV haematological toxicity in 4/28 cases. Complete remission (CR) was recorded in 48% following CF, 79% after Vienna-CHART ($P<0.05$) and 71% after Vienna-CHART+MMC. The overall local failure rates were 73%, 59% and 42% (P=NS) for patients treated by CF, Vienna-CHART and Vienna-CHART+MMC respectively.

Keywords: CHART; mitomycin C; repopulation; potential tumour cell doubling time; hypoxia

Overall treatment time is considered to be one of the major factors influencing the outcome in radiation therapy of squamous cell cancers of the head and neck region (Withers *et al.*, 1988; Overgaard *et al.*, 1988). Owing to tumour cell repopulation during therapy and a short potential tumour cell doubling time (T_{pot}), a long overall treatment time could be a disadvantage and might be the cause of local failure (Wilson *et al.*, 1988; Dobrowsky *et al.*, 1994). To be able to overcome this disadvantage, regimens have been introduced which have a shorter overall treatment time (Saunders *et al.*, 1991). The administration of bioreductive drugs like mitomycin C (MMC) also has a potential advantage, targeting hypoxic tumour cells that can be less radioresponsive (Weissberg *et al.*, 1989). Another possible advantage in using bioreductive drugs with short regimens is that reoxygenation might be incomplete and thus a drug like MMC could be of additional benefit. Following a pilot study using a continuous hyperfractionated accelerated regimen with encouraging results (Dobrowsky *et al.*, 1992) a randomised trial was initiated following approval by the Ethical Commitee of the Medical Faculty of the University of Vienna.

Patients and methods

From October 1990 to March 1994, 90 patients were treated in this study. The median age was 57 years (range 37-76 years), 79 were male and 11 female. All patients had histologically verified squamous cell carcinoma and were referred for primary radiation therapy. Local staging procedures included clinical examination with panendoscopy, computerised tomography (CT) scan, ultrasonography of the head and neck region and bone scan (optional). Distant metastases were excluded by chest radiograph and sonography of the liver. Site of tumour origin was oral cavity in 25 cases, oropharynx in 37 cases, larynx in 15 and hypopharynx in 13 cases. Most patients had stage III or IV disease (75/90) being equally distributed in the three groups (See Table I for site and stage distribution in the three treatment arms).

Patients were stratified for age, gender, stage (T and N) and Karnofsky performance status before randomisation. Informed consent was obtained from all patients. The three treatment arms were: conventional fractionation (CF), consisting of 70 Gy in 35 fractions over 7 weeks; continuous hyperfractionated accelerated radiation therapy (Vienna-

Table I Site of tumour origin and stage distribution

	CF	*Vienna-CHART*	*Vienna-CHART+MMC*
Site			
Oral cavity	10	7	8
Oropharynx	13	13	11
Larynx	5	6	4
Hypopharynx	5	3	5
Stage distribution			
T1			
T2	7	6	6
T3	8	6	7
T4	18	17	16
N0	8	12	10
N1	4	2	3
N2	16	13	11
N3	4	2	3

CF, conventional fractionation; CHART, continuous hyperfractionated accelerated radiation therapy; MMC, mitomycin C.

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CHART), delivering a total dose of 55.3 Gy in 33 fractions on 17 consecutive days, including weekends and holidays. Treatment was typically performed by bilateral portals. Photon beam energy was 6 mV. The dose was prescribed in the midline, with the 90% isodose encompassing all known tumour–lymph node. The maximal total dose to the spinal cord was kept below 40 Gy. This was ensured by treating dorsal parts of the neck by lateral electron portals (energy 9–12 mV) after a dose of 32 Gy to portals including the spinal cord. Treatment was commenced with a single dose of 2.5 Gy on day 1, following treatment planning, and followed by two fractions of 1.65 Gy from day 2 to day 17. The interfraction interval was 6 h or more. The second experimental treatment arm consisted of the same fractionation regimen as above (55.3 Gy in 33 fractions on 17 consecutive days) with the addition of 20 mg m^{-2} mitomycin C (MMC) administered (bolus i.v.) as a single dose on day 5 of radiation therapy (Vienna-CHART + MMC).

Initial tumour response was evaluated 3 months following therapy by clinical examination, CT scan and ultrasonography of the head and neck region. Before, during and following therapy regular blood counts (CBC, including liver and kidney parameters) were examined as well as body weight and Karnofsky performance status. Local mucosal reaction and skin reaction were registered and evaluated regularly during therapy and thereafter every 2–4 weeks until normalisation.

To test statistically the differences found with regard to response rate and tumour progression a chi-square test was performed.

Results

Acute local toxicity was the major side-effect in those patients treated by accelerated fractionation. There was however no difference between these groups given MMC or not. Confluent extensive mucosal reaction (grade 3) occured in 25/29 patients treated by Vienna-CHART, 22/28 treated by Vienna-CHART + MMC but only in 12/33 cases following regular fractionation (CF). The brisk mucosal reaction in patients treated by the accelerated regimens typically started after 2 weeks of radiation therapy and was most distressing for those patients who were treated for tumours of the oral cavity and oropharynx. Those patients where the tongue had been included in the target volume expressed major complaints, and the tongue itself was the region where the mucosal reaction lasted longest. The overall duration of the mucosal reaction in those treated by accelerated therapy was 2–12 weeks (median 5 weeks) and 1–12 weeks (median 6 weeks) following Vienna-CHART and Vienna-CHART + MMC respectively. The total duration of mucositis in patients treated by conventional fractionation was 2–9 weeks (median 7 weeks). Owing to the strong mucosal reaction in the accelerated treatment arms, the majority of patients had a nasogastric tube inserted for nutritional support. In spite of this most patients lost considerable weight during treatment (5–10% of their initial body weight).

The acute effects of the epidermis was not different in the three treatment groups. The duration of the skin reaction was 0–12 weeks (median 3 weeks) in those patients treated by conventional fractionation. Patients undergoing accelerated hyperfractionation experienced a normalisation of the acute skin reaction after 0–4 weeks (median 3 weeks), and those with additional drug (Vienna-CHART + MMC) after 1–7 weeks (median 3 weeks). In the case of epidermal reaction there was no difference in the intensity of erythema.

Haematological toxicity (Grade III/IV) was only recorded in patients receiving MMC. Out of the 28 patients who were in this group, four experienced grade III or IV toxicity. One patient developed leucopenia, the others thrombocytopenia. No active measures had to be taken and the transient bone marrow toxicity resolved within 2–6 weeks, with the nadir being observed 3–4 weeks following MMC administration.

Initial response evaluation was undertaken three months following therapy. Clinical evaluation and CT scan/ultrasonography was performed. Complete remission (CR) was seen in 48% (16/33) patients following regularly fractionated radiation therapy (CF). Patients who were treated by Vienna-CHART and Vienna-CHART + MMC showed a complete remission in 79% (23/29) and 71% (20/28) cases respectively. A statistically significant higher rate of CR in patients treated by V-CHART (but not following V-CHART + MMC) was seen, compared with CF (chi-square test, $P<0.05$). Local recurrent disease after initial CR was seen in 18% of cases after conventional fractionation. Forty-five per cent of those patients experiencing a CR after V-CHART showed a local relapse compared with 21% after Vienna-CHART + MMC. The total relapse rate (local recurrence and progressive persistent disease) was seen in 70%, 59% and 42% after CF, Vienna-CHART and Vienna-CHART + MMC respectively (P = NS).

After the relatively short follow-up period, no significant difference in late effects in the three treatment groups was observed. In some cases, following accelerated therapy, the xerostomy seemed less than that after conventional fractionation. There has been no increase in late effects seen after additional MMC, compared with patients treated by accelerated radiation alone.

Measurement of potential tumour doubling time (T_{pot}) was performed in 28 cases using the bromdeoxyuridine incorporation method. Following an i.v. administration of 250 mg m^{-2} of bromodeoxyuridine, a biopsy of the patient's tumour was examined for cell kinetic studies. The range of T_{pot} was 0.81–16 days (median 3.3 days). Patients treated by conventional fractionation (14 cases) and achieving CR had a median T_{pot} of 4.2 days, whereas those who did not respond or only showed minor response had a T_{pot} of 2.6 days. Fourteen patients were treated by accelerated radiation therapy. T_{pot} did not differ whether CR had been reached or not, the median value was 3 days in complete responders (CR) and in those who had minor response (partial remission).

Discussion

Prolongation of treatment duration is considered to be one of the major causes for treatment failure in radiation therapy of head and neck cancers (Withers *et al.*, 1988; Overgaard *et al.*, 1988). A Danish study was able to estimate the 'loss' of cell kill to a dose equivalent to 4 Gy per week. A split-course regimen was compared with uninterrupted radiation therapy in laryngeal cancer (Overgaard *et al.*, 1988). Tumour proliferation during therapy thus has to be compensated by administation of a higher dose. Cell kinetic studies have shown that many squamous cell cancers of the head and neck region have a very short T_{pot} of only 5 days or less (Wilson *et al.*, 1988). These are the reasons for development of short treatment protocols in head and neck cancers. By using more than one fraction per day it is possible to avoid potential higher toxicity when high single doses are given. The interfraction interval should be long enough to allow for repair of normal tissue damage and it is considered that 6 h interfraction interval should be appropiate. A study from Mount Vernon Hospital, Middlesex, UK was able to demonstrate a benefit for patients with T3 and T4 head and neck cancers when treated by CHART compared with conventional fractionation (Saunders *et al.*, 1991). In this study a total dose of 54 Gy was delivered within only 12 days. It thus seems possible to decrease the total dose to some extent, when short schedules are used, without jeopardising the patients' outcome. In our trial we also added the administration of a bioreductive drug to one of the accelerated treatment arms. The reason for this was that drugs like MMC are more toxic to hypoxic cells (Rauth *et al.*, 1983), which can be present in large squamous cell cancers, and for the potential compensation for impaired reoxygenation if short treatment times are used. Apart from

this, an American study had shown a benefit for patients treated with additional MMC, when conventional fractionation was used (Weissberg *et al.*, 1989). In this study there was no increase in local toxicity. In our study we also did not see any additional local toxicity when MMC was added to accelerated radiation therapy, and only modest or mild haematological toxicity was recorded. From our data we cannot conclude that the addition of MMC has influenced the response rate compared with accelerated radiation therapy alone.

Although the acute mucosal reaction was very intense, it typically starts at the end of therapy and does not negatively influence the delivery of the radiation dose prescribed. We have routinely used an interfraction interval of 6 h or more. Others have described increased acute and late toxicity when shorter intervals were used (Marcial *et al.*, 1987). In our trial the intensity of the mucosal reaction was strong in those patients treated by accelerated therapy but the overall duration of mucositis was quite similar in all three treatment groups. The skin reaction was not considered to be more pronounced in the shorter schedules and also in this respect there was no increase whether MMC had been added to therapy or not. So far there has been no significant increase in late toxicity when acceleration was used, as compared with conventional fractionation.

Our data suggests that initial response rates are improved when patients have been treated by one of the accelerated regimens. Patients treated by V-CHART had a statistically significant increase in CR (chi-square test $P<0.05$) compared with conventional fractionation. There are still small numbers of patients in each treatment group, so that this must not be overinterpreted. This is also reflected by a lack of statistical significance in overall tumour progression (recurrent disease following CR and progressive disease). Treatment failure was recorded in 70% (23/33) patients undergoing conventional fractionation, compared with 59% (17/29) and 42% (12/28) following Vienna-CHART or Vienna-CHART+MMC, indicating an advantage for a short treatment regimen in squamous cell cancer of the head and neck region. More patients will have to be included in the trial to ensure any real difference. The trial has been designed to include more than 300 patients. Following treatment of 50% of these, a statistical analysis, also with regard to survival, is planned.

Shorter schedules should be of benefit when T_{pot} is short. Begg *et al.* (1990) were able to show that patients who had tumours with short T_{pot} had improved outcome when treated by accelerated radiation therapy. Fowler (1992) estimated that patients with short T_{pot} (5 days or less) would benefit from a short treatment time like our regimen. Our cell kinetic data suggests it is important not to treat patients with fast growing tumours by conventional fractionation. However, whether the higher rates of CR after accelerated treatment or treatment of slower growing tumours by CF will be of ultimate benefit with regard to survival will be determined by longer follow-up. Nevertheless, these preliminary results suggest that measurement of cell kinetic parameters, such as T_{pot}, has potential value for selection of patients, with head and neck cancers for individual fractionation schedules in radiation therapy.

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