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Concurrent radiotherapy and chemotherapy in the treatment of locally advanced head and neck cancer

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Background: Concurrent radiotherapy and chemotherapy result in a significant increase of survival with respect to induction chemotherapy followed by radiotherapy or radiotherapy alone. However the concomitant administration of the two modalities produce also a significant increase of toxicity. In order to look for a more tolerated and effective chemoradiation regime, we investigated the feasibility and efficacy of hyperfractionated accelerated irradiation with concurrent protracted venous infusion chemotherapy.

Methods and materials: Sixty five patients with advanced head and neck cancer were treated for the study purpose. Fifty three with gross diseases underwent a definitive treatment, and 12, operated of radical macroscopic resections received an adjuvant treatment. Chemotherapy consisted of intravenous protracted infusion of 5 and 200 mg/m2/day CDDP and 5-FU respectively. Radiotherapy consisted of a split course accelerated hyperfractionation of two 150 cGy (split b.i.d.) or three 100 cGy fractions per day (split t.i.d.) at more than 6 hours interval, for 2 weeks followed, after one week interruption, by 2 to 3 week treatment, with the same fractionation schedule, to a total dose of 60-69 Gy.

Results: Confluent mucositis was the main toxicity. However, with the split course accelerated hyperfractionation radiotherapy, confluent mucositis was tolerable and was the cause of treatment delay of more than 10 days in only 20% of patients. Grade * 3 systemic toxicity occurred only in 9/65 (14%) patients and was never the cause of drug dose reduction. Complete responses were observed in 69% of patients with gross diseases. At a median follow-up of 43.5 months, 45% of patients were alive and free of disease and 38% died of cancer. The 5-year actuarial local regional failure was 35%. The 5-year actuarial disease-specific survival was 50%. Preservation of larynx function was achieved in 47% of alive patients and in 74% of all patients, with advanced tumors of laryngo-pharynx.

Conclusion: The long-term results of this study suggest that this chemoradiation protocol has the potential of achieving a significant improvement over standard therapy while avoiding significant toxicity.

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Treatment of head and neck cancer using CHART with nimorazole: phase I and I studies

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Purpose: In the large UK trial, CHART failed to improve local control rates of head and neck cancer compared with conventional fractionation. A possible explanation is lack of time for tumour cell reoxygenation during a very short treatment time, so a hypoxic-cell sensitiser may be especially beneficial with CHART. Nimorazole is the only such agent to have shown a significant effect in a randomised study in head and neck cancer. Accordingly we studied the combination of CHART and nimorazole.

Methods: A phase I dose-escalation study showed that doses of nimorazole of 1.2g/m2, 0.9g/m2 and 0.6g/m2 before the first, second and third daily fractions of CHART respectively, gave plasma levels consistently above 30 micrograms/ml, without serious toxicity.

A phase II study was then undertaken, using the above dose scheme of nimorazole. The CHART regimen consisted of a total dose of 56.75Gy at the ICRU intersection point, in 36 fractions in 12 days. Sixty-one patients with advanced unresectable squamous carcinoma of the head and neck were enrolled,21 stage III and 40 stage IV.

Results: Six patients failed to receive the prescribed treatment, mostly because of intercurrent medical problems. All patients have been followed for a minimum of 2 years. Loco-regional control by "intention to treat" is 52% (stage III 59%, stage IV 47%). Normal tissue effects were the same as those previously seen with CHART alone. Nimorazole toxicity was limited to nausea and occasionally vomiting, except that one patient died during treatment of a possible encephalopathy atributed to the drug.

Conclusion: Local control is at least 10% better than in comparable groups of patients previouslu treated with CHART, suggesting that further study of the use of nimorazole with accelerated radiotherapy is warranted.

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Oral complications in head and neck cancer patients receiving radiotherapy, with amifostine cytoprotection

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Purpose: Xerostomia, mucositis, and oral candidiasis (OC) are important complications during head and neck radiotherapy (RT). Xerostomia predisposes for the development of OC. In this prospective study these complications were evaluated in 38 patients receiving i.v. amifostine prior to RT, compared to 16 patients receiving RT without amifostine (control group).

Methods: Fifty four patients, with 75% of the salivary glands within the radiation field, entered the study. Thirty eight patients received 500 mg amifostine i.v., prior to each RT fraction, while 16 patients received RT alone. Daily radiation dose ranged between 1.8–2 Gy, and total dose between 50–73 Gy. Subjective xerostomia scales were completed by all patients. Saliva was collected before and after RT in 22 amifostine patients and 3 controls. Mucositis was evaluated using the RTOG criteria. Oral candidiasis was diagnosed according to definitive criteria.

Results: Three patients interrupted amifostine due to nausea. Severe xerostomia was reported by 4/38 (10%) amifostine patients and by 7/16 (44%) controls. Saliva was below 0.1 ml/5 min in 3/22 amifostine patients and in 2/3 controls. Four/38 (10%) amifostine patients and 4/16 controls (25%) completed RT with mucositis grade III. Oral candidiasis was diagnosed in 11/38 (29%) amifostine patients and in 9/16 (56%) controls.

Conclusion: Amifostine reduced xerostomia ($p = 0.01$), salivary dysfunction ($p = 0.09$), and OC ($p = 0.07$). Importantly, the diagnosis of OC is an objective criterion for the beneficial effect of amifostine in the quality of life of the head and neck cancer patients.

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A phase II randomized study of cisplatin (CDDP), raltitrexed (TOM), levofolinic acid (LFA), and 5-fluorouracil (5-FU), or CDDP, methotrexate (MTX), LFA and 5-FU in locally advanced (LAD) or metastatic (M) head and neck cancer (HNC)

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Background: CDDP+MTX+LFA+5-FU is an active regimen in HNC, since it has previously resulted in a response rate of 80% and median overall survival of 21 months (Cancer, 1999). TOM exhibits complementary in vitro activity to CDDP and is active in HNC when combined with LFA and 5-FU (Clin Cancer Res, 1999). We have tested CDDP+TOM+LFA+5-FU in a phase I-II trial in HNC, achieving a very encouraging antitumor activity (Ann Oncol, 2000).

Patients and methods: Patients (pts) with inoperable LAD or M HNC, unpretreated with chemo or radiotherapy, were randomized to receive either CDDP 60 mg/m2 and TOM 2.5 mg/m2 on day 1, LFA 250 mg/m2 and 5-FU 900 mg/m2 on day 2 (Arm A); or CDDP 65 mg/m2 and MTX 500 mg/m2 on day 1, LFA 250 mg/m2 and 5-FU 800 mg/m2 on day 2 (Arm B). Both treatments were repeated every two weeks. Evaluation for tumor response was performed after four cycles. According to Simon two-stage design, with a p1=35% CR rate, at least 7 CR among the first 31 treated pts, and 16 CR among the final sample size of 53 pts were required.

Results: In October 2000, 35 pts were evaluable in each arm and interim analysis was performed. In Arm A, 10 CR and 18 PR were observed, for an overall response (OR) rate of 80% (95% C.I., 63% to 92%). In arm B, 3 CR and 11 PR were observed, for an OR rate of 40% (95% C.I., 24% to 58%). The difference in both CR and OR rate between the two arms was statistically significant ($p=0.03$ and <0.001, respectively). Therefore, the accrual was stopped in Arm B and continued only in Arm A. As of April 2001, 58 pts have been accrued in Arm A, 47 of whom are evaluable for response and toxicity (11 pts too early). Overall, 11 CR (23%) and 24 PR (51%) have been observed in Arm A, for an overall response rate of 74% (95% C.I., 60% to 86%). Neutropenia was the main side effect in both arms (grade 3-4 in 33/23 pts in Arm A/B). Extrahematologic toxicity was mild in both arms; however, 2 pts in Arm B had a toxic death (grade 4 mucositis in one case, grade 4 renal toxicity in the other).

Conclusion: CDDP+TOM+LFA+5-FU has shown significant antitumor activity and manageable toxicity in HNC pts. Final data (which will be