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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

presented at the meeting) are awaited in order to make a decision about further trials with this regimen.

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Exclusive high-dose-rate brachytherapy for oral cavity carcinomas

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Purpose: The important role of brachytherapy in the treatment of oral cavity tumors is well established. However, there is still a lot of controversy about the use of high-dose-rate brachytherapy (HDRBT) for head and neck carcinomas. In this prospective study, we evaluated the efficacy and safety of exclusive HDRBT in patients with oral cavity carcinoma.

Methods and Materials: Were eligible patients with a biopsy proven grade 1 or 2 squamous cell carcinoma or adenocarcinoma of oral cavity stage Tis, T1 or T2, N0, M0. HDR Ir-192 afterloading system was used delivering dose of 40.2 Gy in 12 fractions over 98 hours. The implants technique and dosimetry followed the rules of Paris system with optimisation allowed.

Results: 17 patients were included, 6 of which presented with a lower lip tumor, 4 with carcinoma of the floor of the mouth, 3 with oral tongue tumor, 2 with cancer of the buccal mucosa, one with lower alveolar ridge tumor and one with soft palate tumor. The tumor mean diameter was 2.37 cm. Eleven were T1, 5 were T2 and 1 Tis. All cases were proven by biopsy and there were 16 squamous cell carcinomas and one adenocarcinoma. Of the 16 invasive carcinomas, 12 were grade 1 and 4 were grade 2. In only 4 patients was HDRBT used for a prior treatment failure. For all the others, HDRBT was the first and exclusive treatment.

At the last follow-up, 11 patients were alive without evidence of disease and no toxicity, 1 patient was alive with toxicity, 2 patients were alive but developed a second cancer and 3 patients were deceased (of whom two from atherosclerotic disease). With a median follow-up of 30 months, late toxicity was found in three patients (17.6%): one patient experiencing soft tissue necrosis, one patient suffering a bone necrosis and one other patient neuropathic pain. The soft tissue necrosis was successfully treated with hyperbaric oxygenotherapy.

The local control rate and locoregional control rate are 88.2% and 76.5% respectively. The disease-free survival, the overall survival and the disease-specific survival are respectively 76.5%, 82.4% and 94.1% at 2 years.

Conclusion: In this series, exclusive HDRBT for oral cavity cancers bears no higher risk of toxicity when compared to than LDRBT series. So far, control rate and survival also seem similar.

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Regionally advanced nasopharyngeal carcinoma (NPC): patterns of failure after sequential chemotherapy (CT) and radiotherapy (RT)

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Purpose: To evaluate clinical outcome and pattern of failure in 61 patients (pts) with regionally advanced NPC treated with sequential CT and RT.

Methods: In 1990 a Phase II trial was designed to evaluate feasibility and activity of a regimen including sequential CT and RT. Inclusion criteria: pathological confirmation of NPC; stage (UICC 1987) T-any, N2-3, M0; ECOG PS 0-1. Treatment: 3 cycles of induction CT with epirubicin 70 mg/m2 d1 and cisplatin 100 mg/m2 d1 (recycle 21 d) followed by radiotherapy to nasopharynx (64-70 Gy) and neck (50-70 Gy), with conventional fractionation (1,8-2 Gy/fr, 5 frs/week).

Results: Sixty-one patients were accrued from 2/1990 to 9/1996. Stage according to UICC 1997 was IIb in 13%, III in 33% and IV in 54% of pts. Sex: male 75%; age: median 44 y (range 17-72 y); histology: WHO type 1-2 (11%), WHO type 3 (89%). Sixty pts received 3 cycles of CT, 1 pt 2 cycles due to no response. Toxicity was moderate with minor dose reductions in 4 pts. RT was given to 60 pts. (1 pt. had distant M+ after CT): total dose ranged from 60 to 71.6 Gy (median 66.9 Gy), total duration 40-65 d (median 51 d). Acute toxicity was acceptable with a split prescribed in 26% pts. With a median follow-up of 5.3 y (range 3.6-10.2 y) 44 failures have been observed in 29 pts. Initial failure was local in 10%, regional in 18%, local and regional in 1.6% and distant in 18% of pts. Seven pts were dissected for a neck nodal failure, and 4 were re-irradiated to the primary site for a local failure. At 5 years local control was 83%, regional control 74% and freedom from M+ 70%; overall survival was 62% and disease-free survival (DFS) 52%. Frequently reported late effects included xerostomia in the majority of patients and significant hearing loss in 18 pts.

Conclusions: In our series, freedom from distant metastases and overall survival were similar to values reported recently with more aggressive regimens of combined modality treatment; regional control and DFS were relatively worse probably due to inclusion criteria (N2-N3).

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Analysis of mandibular dose distribution in radiotherapy (RT) for oropharyngeal cancer

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Purpose: Relationship between RT dose and the risk of osteoradionecrosis is well known. However, the dose to the mandible is not routinely assessed in RT for head and neck cancer. Our aim was to analyze the mandibular dose distribution in patients (pts) administered RT for oropharyngeal cancer.

Methods: We examined RT plans in 18 pts treated with bifractionated RT for stage II-IV M0 oropharyngeal cancer. In 17 pts RT dose prescribed in the ICRU point was 74.4 Gy/62 fractions (1.2 Gy bid, 6 h interfraction interval) and 1 pt received 75.6 Gy. The whole dose to the mandibular region was delivered with 6 MV photons. The mandible was contoured manually on CT scans and the point doses at the both mandibular condyles, ascending ramus, mental symphysis, molar and retromolar regions were assessed. Cumulative dose-volume histograms (DVH) were evaluated.

Results: The highest doses were observed in the retromolar regions. The mean percentage doses at the right and left retromolar regions were 101.3% ± 3.8% (range, 90.2-109.1%) and 101.7% ± 2.5% (range, 95.2-105.8%), respectively. Lower doses were seen in ascending ramus (mean right and left ramus: 97.3% ± 8.5% and 97.8% ± 7.6%, respectively), the molar regions (mean right and left molar region: 86.0% ± 13.5% and 88.1% ± 12.9%, respectively), and at the mandibular condyles (mean right and left condyle 72.6% ± 18% and 77.0% ± 16.5%, respectively). The mandible volume ranged from 60.1 cm3 to 110.1 cm3 (mean 82.3 cm3). In all pts the maximum dose absorbed in the mandible was higher then the dose prescribed in the ICRU point and the mean maximum dose absorbed in the mandible was 105.7% ± 2.1% (range 102.4-110.6%). The percentage of mandibular volume receiving a dose higher than prescribed was 28.6% ± 14.9% (range 10.2-58.1%). The DVH area, maximum mandibular doses and retromolar doses did not appear to statistically depend on use of wedge or mandibular volume.

Conclusions: RT for oropharyngeal cancer is associated with high doses to the retromolar mandibular regions (the dose can be higher then prescribed in the ICRU point), ascending ramus and molar regions. Lower doses are absorbed at the condyles and mental symphysis. The single dose point (for example, the ICRU reference point) could be not representative for the mandibular dose.

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Low-dose paclitaxel radiosensitization in locally advanced head and neck cancers

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Introduction: Combined modality treatment with chemotherapy and radiotherapy in locally advanced head and neck cancers is an effective and often the only treatment with a chance of cure. These schedules are usually very intensive and therefore hardly be executed in patients with impaired general condition. An alternative is to use chemotherapeutic agents in low dose as radiosensitizers. In this study we examined the radiosensitizing effect of low dose paclitaxel (Taxol, Bristol-Myers Squibb) in locally advanced head and neck cancer.