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PHASE II STUDY OF MITOXANTRONE IN LOCALLY ADVANCED OR METASTATIC ADENOID CYSTIC CARCINOMAS (ACC) OF THE HEAD AND NECK.

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ACCs are rare and usually slowly progressing tumors. Data on chemotherapy are anecdotal. In 1985 the EORTC HNCCG decided to start a program on phase II studies testing single agents in this disease. Only chemotherapy-naive patients (pts) who are symptomatic or who have rapidly progressive disease are included in these studies. In the present study Mitoxantrone is used at a dose of 14 mg/m^2, once every 3 weeks. Response is evaluated after 2 cycles and both response and toxicity are graded according to WHO criteria.
Twenty-five pts entered the study so far. One was ineligible, 8 are too early and 16 are presently evaluable, 8 males and 8 females, median age of 61 years (range 26-70), and median WHO performance score of 1 (range 0-1). Prior treatment included surgery in 14 pts and radiotherapy in 12. The median number of cycles given was 5 (range 2-22).
Side effects were leucocytopenia in all pts (75% grade 3-4) frequently necessitating dose-reduction and/or treatment delays, thrombocytopenia in 1 (6%), nausea in 11 pts (69%) and vomiting in 4 (24%), alopecia in 9 pts (56%) and grade 1 infections in 6 (38%). One pt developed cardiac toxicity after 5 courses. There were no toxic deaths. Three partial responses were observed (19%) lasting 3-8 months, and 9 stable diseases (60%), median duration 7 months (range 3-20$^+$). This interim analysis suggests that Mitoxantrone may have interesting antitumor activity in this tumortype, when given first-line.

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PHASE II STUDY OF A SHORT COURSE OF WEEKLY CISPLATIN (C) IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA (SCC) OF THE HEAD AND NECK.

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In a phase II study 44 patients (pts) with locally advanced inoperable and radioincurable SCC, 37 males and 7 females, median age 52 years (range 38-72 y), median performance status 1 (0-1) were treated with C at a dose of 80 mg/m^2 weekly for six weeks. C is dissolved in 250 ml 3% hypertonic saline and administered as a 3 hour infusion with standard pre- and posthydration. 5HT$_3$-antagonists are used as antiemetic. Dose reductions are not made. In case of bone marrow depression (BMD) C administration is delayed until recovery. In case of delay > 2 weeks or in case of nephro- or neurotoxicity > grade 1 the pts are taken off study. To date 28 pts are evaluable for response and 34 for toxicity. Six pts achieved a CR and 13 a PR (RR 68%), 6 had SD and 3 PD. All patients were irradiated after completion the C administrations. Median no. of C administrations per patient 5(1-6); median C dose intensity reached 67 mg/m^2/wk (range 40-80 mg/m^2/wk). Five pts completed the 6 courses of treatment without any delay; 6 pts completed 6 courses with 1 and 3 pts with 2 weeks delay; in 7 pts the sixth course was cancelled because of BMD (4 pts), PD (2 pts) or refusal (1 pt); 3 pts received 4 C courses: due to BMD in 2 and PD in 1 pt; 5 pts received 3 C courses (protocol violation in 1 pt) and BMD in 4 pts. After the first C administration 4 pts were taken off study because of CVA 1 pt, ototoxicity 2 pts and nephrotoxicity 1pt; after the second dose 1 pt because of GI toxicity. Toxicities observed in 34 patients: leucocytopenia grade 3 in 11 pts; trombocytopenia grade 3 in 7 and grade 4 in 3 pts; nausea/vomiting grade 3 in 17 pts; nephrotoxicity grade 1 in 5 pts and grade 4 in 1 pt; neurotoxicity grade 1 in 3 pts; ototoxicity grade 2 in 11 and grade 3 in 1 pt. There were no toxic deaths. We conclude that with this short course of single agent C a high dose intensity can be reached yielding a similar response rate as combination regimens in SCC. In general the schedule is well tolerated with the exception of ototoxicity.

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IFOSFAMIDE PLUS CARBOPLATIN FOR THE TREATMENT OF ADVANCED HEAD AND NECK CANCER. PRELIMINARY REPORT.

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From May 1991 to January 1993, 30 patients (pts), male 27, with advanced head and neck squamous cell cancer, HNSCC (larynx 5, amygdala 7, cavum 3, hypofarynx 3, maxylar sinus 3, gena 2, tongue, palate, floor of mouth and salivar gland 1 each), median age 62 years (range 48-74 years), were treated with ifosfamide (IF) 2500 mg/m2, 3 hour IV infusion, days 1-5; mesna IV 20% of IF dose at hour 0 and 2; mesna per os 40% of IF dose at hour 6 and 10, days 1-5, and carboplatin (CRB) 300 mg/m2, 30 minutes IV infusion on day 1. Cycles were repeated every 28 days. Prior therapy was given to 8 pts: surgery 2 and radiotherapy 6. 121 cycles of chemotherapy were given, with a median of 4 cycles/pt. On 23 evaluable pts, 19 objective responses (82.6%) were seen: CR 5 (amygdala 2, maxylar sinus, palate and larynx 1 each), and PR 14. Four pts received radiotherapy after chemotherapy completion and one PR changed to CR. OMS grade III-IV toxicity was seen: leukopenia 6, anemia 1, thrombopenia 1, stomatitis 2 and CNS 1. Median survival time is 7+ months (mo), range 3-19+ mo. 18 pts are still alive. In this preliminary report, IF + CRB chemotherapy combination was well tolerated and achieved a good rate of response.

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PILOT STUDY: A PHASE II CLINICAL TRIAL TO TEST THE ABILITY OF PILOCARPINE TO REDUCE THE ORAL COMPLICATIONS OF RADIOTHERAPY TO THE HEAD AND NECK REGION.

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Oral dryness associated with decreased saliva is a common side effect from external radiation therapy (XRT) to the head and neck region. Xerostomia can develop as both an acute reaction during XRT as well as a chronic reaction which may be permanent. Eight patients, receiving a minimum dose of 5040 rads, entered this clinical trial and received pilocarpine hydrochloride solution. Patients took one teaspoon (5 mg/ml) three times daily, beginning on the day of their first radiation treatment. Salivary function tests, subjective complaints and physical exams were performed before the start of XRT and weekly thereafter. There were no adverse reactions due to the pilocarpine. Seven out of the eight subject (88%) tolerated their course of XRT without a treatment interruption. The expected precipitous fall in resting and stimulated salivary flow rates did not occur in any of the subjects. Saliva yeast counts increased and salivary pH levels modestly decreased over the course of XRT. Our data suggests that pilocarpine may reduce the severity of the effects associated with the radiation induced salivary hypofunction. Patients appeared to have an improved tolerance to the acute oral complications. With better tolerance and improved patient comfort, there should be a lower risk for a treatment break. This is of fundamental importance since protracted XRT courses (associated with treatment breaks) has been correlated with a lowering of local control rates.

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CISPLATIN (CDDP), FLUOROURACIL (FU) AND L-FOLINIC ACID (L-FA) IN ADVANCED HEAD AND NECK CARCINOMA (HNC):AN OUTPATIENT SCHEDULE.

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30 locally advanced or metastatic HNC patients (pts) have been so far included in a phase II trial. The treatment schedule was: FU 375 mg/m2 plus L-FA 100 mg/m2 (4 hs i.v.) followed by CDDP 20 mg/m2 (2 hs i.v.) d 1-5, q 3wks. WHO criteria were used for both clinical response and toxicity evaluation. At present 26 previously untreated pts are evaluable for toxicity and 24 for response. The characteristics of pts were: mean age 56y (range 34-75);mean P.S.(KI) 84(range 70-100);primary site:larinx (7pts),oral cavity (7pts),oropharynx (5pts),nasopharynx (4pts), ipopharynx (2pts),salivar glands (2pts),nasal fossa (1pt),paranasal sinuses (1pt), malar region (1pt). The majority of pts had squamous cell carcinoma (80%). The metastatic sites were cervical nodes (53%) and lung (7%). 24 patients had locoregional disease. We observed 4 CR (mean duration 9.4+mo) and 13 PR (mean duration 6.6+mo) with an ORR of 71%. The median of survival has not been reached yet, while overall mean survival was 10.1+ mo. The most important side effects were G3-4 nausea/vomiting (23%) of pts, G3 diarrhea (8%), G3-4 anemia (12%), G3 leucopenia and thrombocytopenia (1pt), mild nephro- toxicity (23%), moderate fatigue (11%) and no severe stomatitis was seen. The study is still open. These preliminary data seem to show that this schedule is very active in these setting of pts, showing a toxicity at least similar to that of more aggressive schedule.

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THE POTENTIAL FOR HIGH DOSE RATE BRACHYTHERAPY IN HEAD AND NECK CANCER

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This is a report on the implementation of high dose rate (HDR) interstitial brachytherapy as the sole treatment for squamous cell carcinomas in 6 patients; a 66 year-old male with a recurrent 6 cm carcinoma of the upper lip, an 87 year-old male with a recurrent 4 cm carcinoma of the left nasal vestibule extending into the nasal cavity, an 83 year-old female with a 3 cm carcinoma of the tongue, an 82 year-old male with a 2 cm lesion on the buccal mucosa, and 2 patients, each with a neck mass that recurred after two dissections and one to two courses of external beam irradiation. Only the exposed portion of the mass was implanted due to concerns about piercing the carotid artery. In one case, ultrasound was used as an aide to avoid the carotid vessel. Between eight to ten treatments of 450 cGy each were delivered over five days. All brachytherapy treatments were delivered on a BID basis with at least five hours between treatments. The first four have no evidence of disease (NED) at 2-17 month follow-up while the latter two died of systemic disease soon after. No morbidity has been noted.

Based on our initial experience, we have determined that not only was it more convenient to implement HDR brachytherapy, but also more advantageous than LDR brachytherapy. There was no reduction in nursing care, contrary to what is seen with LDR brachytherapy. As well, the short treatment time associated with HDR brachytherapy, was critical in facilitating patient compliance with the placement of lead in strategic locations to diminish the dose received by normal tissue.