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PRIMARY CHEMOTHERAPY WITH CISPLATIN (CDDP) AND EPIRUBICIN (EPI) PLUS RADIOTHERAPY FOR ADVANCED NASOPHARYNGEAL CARCINOMA (NPC).

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Twenty-six consecutive pts (median age 44 yrs, range 19-69) with advanced local regional NPC (undifferentiated, 24; squamous, 2) were prospectively treated with cisplatin (100 mg/sqm) and epirubicin (70 mg/sqm) every 3 weeks for 3 cycles followed by radiotherapy (RT). Advanced local-regional disease was defined, according to the UICC/AJC classification (1987), as any N3 stage (12 pts) or N2 stage with T2 (parapharyngeal involvement), T3 or T4 extension (14 pts). Staging included CT-scan, bone scan, liver sonogram, chest X-ray. All pts are evaluable for toxicity and response.
The CR+PR rate with primary chemotherapy was 92% (95% CI: 75% to 99%), with 3 pts already in CR (12%). RT was able to convert 16 PRs into CRs, with 19 pts eventually free of disease (79%; 95% CI: 58% to 93%). Two pts progressed during chemotherapy, while the other 5 pts in PR after radiotherapy were rendered disease free by surgery. Side effects of chemotherapy were vomiting (92%), alopecia (92%), grade 2 and 3 myelosuppression (27%). No severe tissue fibrosis was observed.
Cisplatin plus epirubicin is a highly active regimen in advanced NPC. The effectiveness of primary chemotherapy needs to be defined within prospective randomized trials.

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LONG-TERM EXPERIENCE WITH CISPLATIN-BASED INDUCTION CHEMOTHERAPY AND CONCOMITANT CHEMORADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCER (HNC).

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From 1987-89 we tested 3 different induction chemotherapy regimens on 92 patients [pts]. 33 pts received 2 cycles of PBM (Cisplatin [P], Bleomycin [B], Methotrexate [M]), 31 PFL (Cisplatin, 5-FU [F] Leucovorin [L]) and 28 PFL-MP (Methotrexate [M], Piritrexim [P]. Local therapy consisted of optional surgery and concomitant chemoradiotherapy [X] with 5-FU [F], Hydroxyurea [H] [FHX]. The overall response rate to the induction therapy was 77% with 29% CR. At a median follow-up of 3.86 years [yrs] the median overall survival is 26 months. Medium survival for the PFL group has not yet been reached. Estimates alive at 4 yrs are 23% (±8) for PBM, 54% (±9) for PFL, and 47% (±10) for PFL-MP. The median time to progression [TTP] is not reached. The estimates at 4 yrs failure free are 58 % (±6) overall, and 35% (±9) for PBM, 68% (±9) for PFL and 63% (±10) for PFL-MP. Most recurrences occured within the first 2 yrs, (0.5-33 mo). 8 second malignancies occured at a median of 2.7 yrs (0.7-4.3 yrs). The local failure rates were 30%, 30% and 17 % for PBM, PFL and PFL-MP respectively. A striking difference was found in the distant failures with 27% for PBM vs only 3% and 14% for PFL and PFL-MP. PFL is an active regimen with a low rate of distant failures. Chemoradiotherapy with FHX is effective in controlling local disease. Second malignancies are the major risk factor after 2 yrs.

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PRIMARY (NEOADJUVANT) COMBINED MODALITY THERAPY IN THE MANAGEMENT OF LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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Our phase II study had two main goals: 1) to assess the results, in terms of OR rates, of the neoadjuvant combined therapy and 2) to substantially reduce the extent of surgery in the treatment of locally advanced squamous cell carcinomas (SCC) of the head and neck. The patients (pts) were divided into two groups: the first included pts with SCC of the oral cavity, oropharynx and hypopharynx (HNC group) and the second included pts with laryngeal SCC (LC group). The primary chemotherapy (both for HNC and for LC) was the classical Al Sarraf's Regimen repeated three times every 3 weeks (for HNC a radiation therapy up to 30 Gy was performed immediately after the first chemotherapy cycle). The clinical response was evaluated after at least 3 complete cycles of chemotherapy. The pts accrual was from February '90 to December '92. The study included 35 pts with HNC, 27 of whom (25 men and 2 women; mean age: 54.4 years, range 31-84; 1 pt stage II, 7 stage III, 19 stage IV, performance status ECOG 0-2) could be evaluated at February '93. The study also included 16 pts with LC, 13 of whom (12 men and 1 woman; mean age: 58.1 years, range 40-78; 1 pt stage II, 6 stage III, 6 stage IV, performance status 0-1) could be evaluated at February '93. In HNC pts an OR was achieved in 25/27 (92.6%): CR 11/27 (40.7%), PR 14/27 (51.9%); in LC pts an OR was achieved in 12/13 (92.3%): CR 7/13 (53.8%), PR 5/13 (38.5%). The median follow-up time was 6. months (range 3.1-33) for HNC pts and 7. months (range 2.6-33.5) for LC pts. At February '93, 18/27 (66.7%) HNC pts, all in OR (12 CR, 6 PR) and 12/13 (92.3%) LC pts, 11 in OR (8 CR, 3 PR) and 1 in PD are alive. As for severe toxicity, there were 11 hematological, 12 gastrointestinal, 1 neurological, 1 cardiac. As far as the second goal of our study is concerned, we can summarize our results by scoring the reduction of the extent of surgery made possible by neoadjuvant chemotherapy versus the standard local therapy which would have been entailed to each pt. Among the HNC pts we have obtained: 13/27 pts with score 3 (very highly reduced extent of surgery and/or function preservation), 6/27 pts with score 2 (highly reduced extent ...), 1 /27 with score 1 (moderately reduced extent ...) and 7/27 with score 0 (non reduced extent ...), and, among the 5 LC pts randomly submitted to surgery: 1 pt with score 3, 3 pts with score 2 and 1 pt with score 0. (Work supported by C.N.R., Rome, A.P. "Clinical Applications of Oncological Research", Contract No. 92.02211.PF39)

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INTENSIFIED AND ACCELERATED CONCOMITANT CHEMORADIOTHERAPY AND G-CSF FOR LOCALLY ADVANCED HEAD AND NECK CANCER

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In order to intensify concomitant chemoradiotherapy with myelosuppresion and mucositis as the main toxicities we added G-CSF days 6-12 (5ug/kg) in a dose escalation study. We modified our previously reported regimen of P-FHX week on/week off (Cisplatin [P], 5-Fluorouracil [F], Hydroxyurea [H], daily radiation [X]) with dose escalation of Hydroxyurea up to 2500 mg/day. Subsequently we instituted accelerated radiotherapy of 150 cGy bid. Of 29 patients (pts) 15 achieved a complete response (CR). At the 2500mg dose level of Hydroxyurea grade 4 neutropenia occured, grade 4 mucositis at a dose of 2000 mg. Both cumulative myelosuppression and mucositis were noted in cycles 3-7. Hyperfractionated radiation increased acute skin toxicity and mucosits. Compared to our historic control, G-CSF allowed for doubling of the Hydroxyurea-dose and reduced mucositis. Hyperfractionaton may reduce cumulative toxicity and shorten the treatment duration.

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SIMULTANEUOS CHEMOTHERAPY AND RADIOTHERAPY FOR ADVANCED HEAD AND NECK CANCER

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We report a phase II study of simultaneous chemotherapy and radiotherapy as initial treatment for patients with advanced tumours of the oral cavity and oropharynx. 31 patients were entered. Chemotherapy consisted of 3 cycles of Cisplatin(100mg/m²day 1) and 5-Fluorouracil(1000mg/m²days 1 to 5). Radiotherapy began with the second cycle up to a dose of 30Gy. Patients underwent surgery and postoperative radiotherapy was given (30 Gy). 25 patients achieved clinical response (80%) and 16 complete respose (52%). The pathological complete response (PCR) was 39%. The median survival was 10.7 months. Only 1 PCR patient has relapsed. The median survivalfor PCR and non-PCR was 16.5 months and 8.2 months respectively ($p<0.05$). Severe mucositis occurred in 16 patients. Mean wheight loss was 8%. 11 patients required additional hospitalization for parenteral nutrition. CONCLUSION. This regimen achieves a high rate of PCR. Toxicity was important but accetable with supportive care.

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PREVENTION OF SECOND PRIMARY TUMORS WITH ETRETINATE IN SQUAMOUS CELL CARCINOMA OF ORAL CAVITY AND OROPHARYNX. RESULTS OF A DOUBLE-BLIND RANDOMIZED STUDY

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Patients who are cured from head and neck carcinomas remain at risk for developping a second primary in the head and neck area. It is now clear that retinoids exert a prophylactic action on the development of epithelial cancers, when tested on laboratory animals and on human malignant lesions.
We prospectively studied 316 patients who developed squamous cell carcinoma of the head and neck, classified as T1/T2, N0/N1 ≤ 3cm, M0 according to the UICC TNM classification. Patients were randomly assigned to receive orally double blind, either etretinate (a loading dose of 50 mg per day the first month, followed by a dose of 25 mg per day the following months) or placebo for 24 months. Adjuvant treatment began no later than 15 days from the onset of surgery and / or radiotherapy. The 5-year survival rates as well as the 5-year disease free survival rates are similar in the two groups. There are no differences regarding either local, regional or metastasis relapses. After a median follow-up of 41 months (0-81), twenty eight patients in the etretinate group and twenty nine in the placebo one, experienced a second cancer, with respectively 12 and 13 in the head and neck region. Thirty three percent of the patients in the etretinate group stopped definitively their adjuvant treatment, against 23 % for the placebo group, mainly because of toxicity ($p < 0.005$). Etretinate, a second-generation retinoid, does not prevent second primary tumors in patients who have been treated for squamous cell carcinoma of oral cavity and oropharynx.