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A PHASE II STUDY OF TAXOTERE IN PATIENTS WITH ADVANCED HEAD AND NECK CANCER

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Taxotere, a semisynthetic analogue of Taxol, is a potentially important chemotherapeutic agent for the treatment of cancer. In preclinical testing, Taxotere was active against various tumor models. 42 patients (pts) with bidimensionally measurable locally advanced, unresectable, or metastatic squamous cell carcinoma of the head and neck, were treated with Taxotere 100 mg/m^2 as a 1 hour infusion every 3 weeks. Pts characteristics were as follows : 22 males, 7 females, 13 yet unknown ; median WHO performance status 1 (0-2) ; median age 55 years (39-74) ; previous radiotherapy 22 pts, previous neoadjuvant chemotherapy 8 pts. Bidimensionally measurable sites included : primary tumor 12, lymph nodes 12, soft tissue 8, lung 1. The median number of cycles administered was 2 (1-8). CTC grade 3 and 4 toxicities were reported, including neutropenia in 18 pts, asthenia in 3 pts, stomatitis in 2 pts. Hypersensitivity reactions occured in 6 pts. Grade 2 alopecia was observed in 15 pts. Concerning efficacy, results are as follows : 1 CR, 10 PR (4 to be confirmed for duration), 4 SD, 10 progression, in 25 pts evaluated. 2 pts were not eligible, 1 was not evaluable and 14 are too early for evaluation yet.
Taxotere given at this dosage and with this schedule appears to have a high level of activity in patients with advanced head and neck carcinoma.

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A PHASE III STUDY COMPARING INDUCTION CHEMOTHERAPY BY CARBOPLATIN (CBDCA) AND 5 FLUOROURACILE (5 FU) BEFORE LOCOREGIONAL TREATMENT (LRT) VERSUS LOCOREGIONAL TREATMENT ALONE IN HEAD AND NECK CARCINOMAS.

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A phase III stratified randomized multicentre trial comparing induction chemotherapy (CT) prior to LRT (surgery + radiotherapy (RT) or RT alone) versus LRT alone was conducted from 01/88 to 07/91. Of the 324 randomized patients (pts) 300 could be analysed : oral cavity 79, oropharynx 106, pharyngolarynx 115. The characteristics of pts were well balanced between CT-LRT arm (150 pts) and LRT arm (150 pts). CT consisted of CBDCA 400 mg/m2 day 1 and 5 FU 1 g/m^2 day 1 to day 5 every 3 weeks, for 3 cycles.

In the CT-LRT arm, 143 pts were evaluable for efficacy and toxicity : objective response rate was 61 % and complete response rate 30 %, the main toxicity was haematological with 19 % thrombocytopenia and 24 % neutropenia grade 3-4. Three toxic deaths were recorded (1cardiac toxicity - 2 septicemia). Conservative treatment was performed in 57 % of pts in the CT-LRT arm versus 24 % of pts in the LRT arm (p = 0.001). CT therefore allowed organ/function preservation in 33 % of patients who otherwise would have undergone a mutilating surgery.

With a median follow-up of 25 months we observed in the CT- LRT arm and LRT arm respectively a locoregional relapse rate of 35 % and 25 % p = 0.04. No difference was detected for metastases or second localisation rates .

At 4 years, disease free survival for the CT - LRT arm and for the LRT alone arm were 33 % and 30 % respectively (NS). Overall survival was 56 % and 46 %, respectively in the two arms of the study (NS).

Induction CT by CBDCA - 5 FU appears to improve the organ/function preservation rate of 33 % without jeopardizing the long term survival.

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COMBINED BIFRACTIONATED RADIOTHERAPY AND CDDP-5FU CHEMOTHERAPY (BIRCF) IN LOCALLY ADVANCED INOPERABLE PHARYNGEAL CARCINOMAS - a phase II study.

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A Cooperative Group of 4 French Cancer Centers initiates a phase II study to test feasibility and rate of local control at 6 months obtained by a pilot chemo-radiotherapy protocol for advanced carcinomas of pharynx (oropharynx, hypopharynx). Eligibility criteria include KPS≥70, and acceptable renal, cardiac, and blood parameters. Unresectable, not previously treated, stage IV pharyngeal tumors are included, regardless of lymph nodes status. Radiotherapy of primary tumor and satellite nodes is delivered by 2 parallel opposed lateral fields, Co60 or 5-6 MV photons, 2 fractions of 1.2 Gy/day, 5 days a week, with no interruption. Total tumor dose: 80.4 Gy (in 46 days). Spinal cord reduction at 40.8 Gy (complement with 7-10 MeV electrons, 1 fraction/day, 2 Gy/fr.). Supra-clavicular irradiation: 1 ant. field, 1 fraction/day, 2 Gy/fr., total dose 50 Gy + e- complement. Chemotherapy: 3 cycles, at D1, D22, and D43. CDDP: 100 mg/m^2 D1; 5FU: 5-day continuous infusion at 750 mg/m^2/day (D2->D6) with pharmacokinetic adaptation of dose at D4. Patients are hospitalized during treatment, with enteral nutritional support (naso-gastric sound before D14) and active prevention of mucositis. Preliminary inclusions (10 patients) showed acceptable acute toxicity, with grade 3 mucositis lasting less than 10 days, grade 3 transient neutropenia and/or thrombocytopenia in 3 cases, and no disturbance in treatment course, particularly no break during irradiation. High rate of complete tumor response at the end of combined treatment has been achieved. However, our main endpoint will be the rate of local control at 6 months. A phase III multicentric randomized study should be initiated whether further results confirm feasibility and efficiency of this protocol.

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MULTI-CYCLE HIGH DOSE CHEMOTHERAPY WITH PERIPHERAL STEM CELLS TRANSPLANT IN NASOPHARYNGEAL CARCINOMA

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Eleven nasopharyngeal carcinoma patients with metastatic or uncontrolled local regional disease were enrolled in a protocol consisting of two standard dose induction cycles of cisplatin, 5FU and leucovorin followed by two high dose intensification cycles of cisplatin 150 mg/M^2, cyclophosphamide 4.5 gm/M^2 and VP16 900 mg/M^2 given in three days. A third cycle of high dose non-cross resistant cycle of thiotepa 250 mg/M^2 and mitoxantrone 60 mg/M^2 was given for patients with metastatic disease. Peripheral stem cells were collected after the second cycles of standard dose chemotherapy with G-CSF priming. All patients received G-CSF and peripheral stem cells transplant 2 days after high dose chemotherapy. Median days to neutrophil count of 100 and platelet count of 20,000 were 6 and 9 days respectively. All patients were evaluable and the lead follow-up is now 24 months. There were 5 complete responses (CR) and 6 partial responses (PR). One of the partial response was converted to a complete response after local surgery in the nasopharynx. All except one of the CR patients are alive and well with the longest survival so far at 17 months. Two toxic deaths occurred within 60 days of treatment, both from VOD and hepatitis B reactivation. Complete response sites include extensive bone marrow disease (all have over 10 lesions), liver and lung disease. Because of the extremely poor prognostic characters of this group of patients, it could be speculated that about 50% of these patients, after receiving multiple cycles of high dose chemotherapy, would be able to have sustainable complete remission.

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CARBOPLATIN(C),5-FU(F),AND LEUCOVORIN(L) IN PATIENTS WITH RECURRENT SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCC H&N)

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Fifty-four patients with recurrent SCC H&N were treated with combination chemotherapy.There were 43 males and 11 females with median age of 55 years(range,43-67 years).All pts were ECOG PS 1-2.Primary tumor site included nasopharynx in 2,oral cavity in 10,oropharynx in 5,larynx in 22,hypopharynx in 12,and paranasal sinuses in 3 pts.Chemotherapy consisted of C 400 mg/sqm,day 1,F 400 mg/sqm,days 1-5 and L 100 mg/sqm,days 1-5.Cycles were repeated to a total of 6 cycles or until tumor progressed. We observed 7(13%) CR and 12(22%) PR,while 11(20%) pts had SD.24(47%) pts had PD.All 7(13%) CRs were pathologica confirmed.Overall response rate was 35% with median survival of 8.2 months.Two groups of toxicities(ECOG) were observed:hematological and gastrointestinal.Platelet nadir and mucositis were the most common finding.We have observed neither treatment-related deaths nor grade 4 toxicity.Only 11(20%) pts experienced grade 3 toxicity. This combination chemotherapy is well tolerated with less toxicity than other platinum-based regimens used in similar patients,and with response rates obtained warrant further studies with this regimen in a randomized fashion

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RECOVERY OF SALIVARY GLAND FUNCTION FOLLOWING RADICAL RADIOTHERAPY FOR HEAD AND NECK CANCER.

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Salivary gland function has been studied before, during and after radiotherapy in 47 patients receiving treatment for head and neck cancer. Of these 37 were treated by the CHART schedule and 10 received conventionally fractionated radiotherapy to a dose of 66 Gy delivered over 6-7 weeks.

The salivary flow markedly diminishes in the first 2 weeks following the commencement of radiotherapy. Some degree of functional recovery is seen to commence 6 to 9 months following treatment and continues out to at least 21 months and we continue to study our patients in follow up. Parotid glands not fully included in the treatment volume or receiving less than the tumour dose show a relatively greater ability to recover function. Of particular interest is the finding of a greater recovery of function in patients treated by CHART as compared to similar cases receiving conventionally fractionated radiotherapy.