533

MANIPULATION OF THE PERIOPERATIVE IMMUNOLOGIC STATE IN PATIENTS WITH COLORECTAL TUMORS.

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For a long time we have known that surgical stress is often associated to a temporary acquired immune suppression that can potentially increase the risk for postoperative infectious complications and, in cancer patients, for metastasis dissemination and disease recurrences.
Speculations about detrimental effects of surgery on immunologic antitumor mechanisms were recently confirmed by experimental tumor models demonstrating that 1) a surgical procedure which includes entry into the abdominal cavity results clearly in augmented tumor growth (Eggermont et al., Surgery 102:71-78, 1987); 2) surgical stress can lead to increased rates of primary tumor, as well as to increased incidence, size, and rapidity of metastasis development (Pollock: Diss Abstr Int 51(6):2809, 1990).
Our research is based on these rationals, in order to prevent the acquired immune suppression and the suppression of antitumor response and to reduce the postoperative incidence of micrometastases.
We treated 40 patients who underwent surgery for colorectal cancer with interferon beta (IFN-ß). Patients with Dukes'B2-C stage of the disease,(who are statistically at risk for relapses due to microscopic dissemination of metastases), were eligible for this study. They were divided into three groups (20 patients each, sex and age matched): the first group was treated with 3 millions of IFN-ß (Frone, Serono), the second group with or 300,000 units of IFN-ß, while the control group with the placebo. The IFN-ß and the placebo were administered to the patients daily by the intramuscular route for 14 days starting 7 days before surgery and then TIW for six months.
Immunological monitoring (including the phenotypic analysis of the main circulating cell subsets by laser cytometer and the determination of circulating levels of soluble markers, i.e. sIL-2R, sCD8, ß2-microglobulin) was performed before surgery, at 7, 30, 90 and 180 days after surgery.
Preliminary results suggest that the use of conventional dosages (3MU) of IFN may be counterproductive, because they are immunodepressant and they delay surgical recovery of patients. Indeed some patients showed characteristic flu-like symptoms, as asthenia, mild nausea, anorexia, arthro-myalgias, but seldomly; they required treatment with paracetamol. Immunologic impairment involved cytotoxic (NK and CTL) cells, the recovery of which started 30 days after surgery, compared to the 15 days of the control group.
In contrast, the use of low doses of IFN (0.3 MU) enhanced the host immune responsiveness, present 14 days after surgery. The period for surgical recovery was normal and patients had no side effect by IFN.

534

SURGERY ALONE VERSUS PREOPERATIVE RADIOTHERAPY OR RADIO-CHEMOTHERAPY IN OPERABLE RECTAL CANCER: A COMPARISON OF PATHOLOGICAL STAGING.

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From 1989 patients diagnosed of operable rectal cancer are distributed in two groups: Group A (n = 44 pts), surgery and adjuvant treatment for stage B2-C (modified Duke's); Group B (n= 23 pts), preoperative radiotherapy with megavoltage energy equipment, with a total dose of 45 Gy to the pelvis, at 1.8 Gy/day, in 5 weeks; surgery is performed 4-6 weeks after radiotherapy. From 1991, 5-Fluorouracil (300 mg/sqm/day iv) was given concomitantly with preoperative radiotherapy for days 1-5 and 20-25 (Group C, n = 23 pts)). **Results:** Treatment-mortality: Group A, 0%; Group B, 4% (1 pt died of radiation enteritis); Group C, 0%. Unresectable tumor: Group A, 14%; Group B, 9%; Group C, 22%. Without residual microscopic tumor: Group A, 0%; Group B, 4%; Group C, 13%. Stage A-B1: Group A, 14%; Group B, 35%; Group C, 52%. Stage B2: Group A, 29%; Group B, 26%; Group C, 13%. Stage C: Group A, 43%; Group B, 22%; Group C, 0%. Hematological toxicity was minimal (grade 1-2). Neoadjuvant radio-chemotherapy did not compromise operability. **CONCLUSIONS:** Preoperative radio-chemotherapy is effective for dowstaging of the rectal cancer, with acceptable toxicity and without increase in surgery complications. It is necessary a longer follow-up to evaluate if this treatment scheme improves the local control and survival.

535

TAXOTERE IN THE TREATMENT OF ADVANCED COLORECTAL CARCINOMA. Sternberg C.N., Ten Bokkel Huinink W., Kaye S., Bruntsch U., van Oosterom A.T., Pavlidis N., Robinson E., Clavel M., Franklin H., Wanders J. for the EORTC Early Clinical Trials Group/NDDD (Amsterdam) and N. Le Bail, M. Bayssas, Rhone-Poulenc Rorer, France.

Colorectal carcinoma is one of the most frequent malignancies in Europe. Few effective treatment options are available for patients with advanced disease. Taxotere, a new semisynthetic analogue of Taxol, is a potentially important chemotherapeutic agent for the treatment of cancer.In preclinical testing, Taxotere was active against C38, C51, and C26 colon tumors. 37 patients (pts) with bidimensionally measurable advanced adenocarcinoma of the colon were treated with Taxotere 100 mg/m2 every 3 weeks as a 1 hour infusion without premedication for potential hypersensitivity. Pt characteristics included: 23 males, 14 females, median age 58 (41-75 years), WHO performance status 1 (0-2), prior chemotherapy in 4 pts, and prior RT in 8 pts. Bidimensionally measurable disease sites included: lung 9, liver 23, lymph nodes and abdominal/peritoneal masses 10, mediastinal nodes 2, and sc nodes in 1. The median no. of cycles was 2 (range 1-6). 29 pts currently are evaluable for response. 1 pt achieved a PR, 8 had stable disease, 20 had progression. Hypersensitivity reactions occurred in 12 pts. CTC grade 3 and 4 toxicities included: neutropenia in 26 pts, gastrointestinal effects in 2 pts, and fatigue in 6 pts. Taxotere, given at this dosage and schedule, does not appear to be active in the treatment of colorectal carcinoma.

536

RADIOTHERAPY ALONE OR WITH CONCOMITANT CHEMOTHERAPY IN TREATMENT OF ADVANCED ANAL CARCINOMA
RESULTS OF A RANDOMIZED PHASE II TRIAL

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Since January 1987 60 patients with T3/T4 or N pos.anal carcinoma have been randomized to radiotherapy alone or with concomitant chemotherapy.Radiotherapy consisted of external beam irradiation of 45 GY/5 weeks with a daily dose of 1.8 GY.After a rest period of 6 weeks patients with a clinically complete or partial remission received a boost of 15 GY resp.20 GY.Chemotherapy was given as a single dose of Mitomycin C 15 mg/m² day 1 and Fluorouracil 750 mg/m² as continuous infusion day 1-5 and 29-33. Surgery during primary treatment was reserved for patients with no change or progression.
For early toxicity skin reaction grade III 51% vs.53% and diarrhea grade III 6,9% vs.10,7% didn't show much difference.Treatment was never stopped due to undue toxicity.A slight increase of late toxicity as rectel stenosis,ano-rectal damage and rectal bleeding was seen. 86% of all patients experienced a complete response,of these 28% with additional surgery.
The trial is continued as a phase III trial.

Other Gastro-intestinal Tumours

537

A PROSPECTIVE STUDY OF COMBINED INTRALUMINAL BRACHYTHERAPY (ILB) AND EXTERNAL BEAM RADIOTHERAPY (EBRT) IN LOCALLY ADVANCED ESOPHAGEAL CANCER.

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From 1987 to 1992, 105 patients with irresectable esophageal cancer were treated with a full course of ILB and EBRT, to study the efficacy of this regimen with respect to palliation of symptoms. Treatment consisted of ILB (Cs-137, 7 Gy) on day 1, followed by 40 Gy EBRT (15 fx) on day 8, and ILB (6 Gy) on day 37. Pre-treatment dysphagia-scores (WHO classification) were: 0:11%, 1:19%, 2:32%, 3:25% and 4:13%. Clinical staging was based on endoscopy, endosonography (80%), radiography (70%) and CT-scan (40%). Most patients had T3 tumours (63%) or T4 tumours (26%) (UICC 1987). Peri-esophageal lymph nodes were detected in 90%, and coeliac nodes in 21% of patients. Results of treatment: The mean follow-up period is 36 ms (12-70 ms). Mean dysphagia scores post-treatment were: 0:55%; 1:25%; 2:14%; 3: 8% and 4:4%. Pain symptoms improved in 55% of patients. The median survival was 10 months. Local and distant recurrences occurred in 30% and 41% of patients, respectively. The incidence of local recurrences raised from 14% in No-patients to 67% in patients with more than 5 nodes (p=0.0001). Complications: Benign stenosis and fistulas occurred in 15% and 4% of patients respectively, and (chronic) ulceration in 45% of patients. An endoprosthesis for local recurrence was required in 21% of patients. Conclusion: A good palliation of symptoms is achieved in a short treatment period, but ulceration requiring medication is seen in many patients.

538

EARLY DELAYED GASTRIC EMPTYING AFTER ESOPHAGEAL SUBSTITUTION: IS THE PYLORIC SPHINCTER TO BLAME?

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Whether the occurrence of delayed gastric emptying following esophageal substitution with the stomach is influenced by a pyloroplasty, or by the size of the gastric remnant, was retrospectively studied. From 1983 through 1992 116 patients had esophageal resection for cancer (30 days mortality 3.5%) and substitution with either the entire or the distal 2/3 of the stomach. Swallowing studies were done the 6th postoperative day in order to ensure gastric emptying, so oral feeding could be started. Persistent delayed gastric emptying (lasting >2 weeks) was treated by endoscopic balloon dilatation. Follow-up was complete in 101 pts. In 38 cases the entire stomach was used for continuity restoration. Delayed emptying was seen in 4 of the 8 pts (50%) with and in 40% of the 30 pts without pyloroplasty. In 63 pts the distal 2/3 of the stomach was used. Delayed emptying was encounterd in 14.3% of the 21 pts with and in 16.6% of 42 pts without a pyloroplasty. This difference was only significantly determined by the size of the gastric substitute ($p<0.05$). Pyloroplasty does not prevent delayed emptying after gastric replacement. Only the size of the gastric substitute is decisive. The use of a small gastric tube seems essential in preventing delayed gastric emptying.