243 PUBLICATION

Severe toxicity of a standard 5-FU/Leucovorin combination in patients with colorectal cancer: A prospective study

M. Tsalic[1], G. Bar-Sela[1], N. Menashe[1], B. Vizel[1], N. Haim[1,2]. [1]Rambam Medical Center, Oncology, Haifa; [2]Technion, Israel Institute of Technology, Faculty of Medicine, Haifa, Israel

Purpose: To prospectively evaluate: a) the incidence of severe side effects subsequent to treatment with 5-FU/Leucovorin combination (425/20 mg/m^2, IV bolus day 1–5, q 4 weeks) and b) the characteristics of patients developing such toxicity.

Methods: Between January 1995 and December 1998 227 patients with colorectal adenocarcinoma received 5-FU/Leucovorin (95 due to metastatic disease and 132 as an adjuvant therapy). There were 129 males and 98 females (age 26–87, median 65 yrs). 24 patients were given prior adjuvant pelvic irradiation. Severe side effects were defined as those requiring hospitalization.

Results: 39 patients (17%) were hospitalized due to side effects. Patients characteristics in this group included: M/F = 18/21 (vs 111/77 in the remaining patients); age: 35–82 (median 71); WHO PS: 0–2 (median 1); 15 patients received adjuvant therapy and 24 were treated for metastatic disease. 25 of them (64%) were hospitalized due to side effects after the first cycle, 6 after the second cycle and the remaining patients after cycles 3–5. The duration of hospitalization ranged between 2–28 days (median 7). Major toxicity included: grade III & IV diarrhea in 22 patients (9.7% of the entire group), grade III & IV mucositis in 21 patients (9%), neutropenic fever that required IV antibiotics in 24 patients (10%), anemia requiring RBC transfusion in 7 patients (3%) and thrombocytopenia requiring platelets transfusion in one patient. Four patients developed small bowel obstruction that did not require surgery. There were 3 drug-related deaths (1.3%). All three patients had neutropenic fever and grade IV diarrhea.

Conclusion: The 5-FU combination used in this study could be associated with severe toxicity which usually develops after the first cycle. Therefore, dose reduction during the first cycle should be considered.

244 PUBLICATION

Tyrosine phosphatases in integrin-mediated cell adhesion to collagen under static and dynamic flow conditions

J. Haier[1], M. Nasralla[1], G.L. Nicolson[1]. [1]Inst. f. Mol. Medicine, Huntington Beach, CA, United States

Problem: Integrin-mediated cell adhesion is an important determinant of organ-specific metastasis. Distinct intracellular events during the adhesion of carcinoma cells to host organs may be required. These adhesive interactions induce various functional cell responses, including tyrosine phosphorylation and subsequent activation of signaling cascades. We examined whether protein tyrosine phosphatases (PTP) are also involved in cell adhesion and its stabilization.

Methods: Static adhesion assays were performed using fluorescence-labeled HT-29 colon carcinoma cells in microtiter plates. Dynamic adhesion was evaluated with a parallel plate laminar flow chamber. Wall shear adhesion threshold (WSAT), dynamic adhesion rate (DAR) and adhesion stabilization rate (ASR) were determined to differentiate initial adhesion and its stabilization. Cells were pre-treated with phenyl-arsine oxide (PAO) or ortho-vanadate (VA) which inhibit PTP.

Results: Pretreatment with PTP inhibitors abolished cell adhesion under static conditions and interfered with dynamic adhesion in a dose-dependent manner. Low concentrations of PAO lead to significantly higher WSAT and increased cell crawling, whereas higher concen-trations significantly reduced the amount of adherent cells under flow conditions and DAR. However, ASR was not altered by PAO pretreatment.

Conclusions: Our results suggested that PTP are substantially involved in the regulation of integrin-mediated cell adhesion to ECM components. Experiments under flow conditions revealed that PTP take part in early events of cell adhesion.

245 PUBLICATION

Randomized trial of 5-Fluorouracil (5-FU)-Levamisol (LEV) versus 5FU-LEV-Leucovorin (LV) in patients with colorrectal cancer stage II and III. Eigth years results

A. Murias[2], J. Aguiar[1], U. Bohn[1], F. Molano[2], J. Almenarez[2], I. García[2], J.C. Díaz-Chico[3]. [1]Hospital Nuestra Señora del Pino; [2]Hospital Insular; [3]University of Las Palmas, Spain

Colorrectal cancer is the second most common cancer in males and the third in females. The standar adyuvant treatment for patients with colorrectal cancer on stage II and III are the combinations of 5-FU, Levamisol and 5-FU, Leucovorin.

The aim of the study was to determin the efficacy of Leucovorin associated with 5-FU and Levamisol.

Features of patients: From March 1992 to April 1995, 200 patients were included and 179 were evaluable. The median age was 59 years (range 30–75 y). The distribution shown: Colon: 105 and Rectum: 74. Stage II: 81 and stage III: 98. In all cases radical surgery was performed. Those patients with rectal carcinoma received radiotherapy (44 Gys).

Scheme of treatment: The patients were randomized in two groups: Group A: 5-FU – LEV and Group B: 5-FU – LEV – LV. Both arms were well balanced. The treatment was given montly during one year. The first cycle of chemotherapy was administered daily per 5 days. Then after the treatment was given one day montly. A: 5-FU 370 mg/M2 i.v. day 1 Levamisol 150 mg daily × 3 every 2 weeks. B: 5-FU 370 mg/M2 i.v. day 1. Levamisol 150 mg daily × 3. every 2 weeks and Leucovorin 200 mg i.v. 1 hour before 5-FU.

Results: In general the treatments were well tolerated. Grade 3–4 toxicity were not seen. The median follow up was 42 months (range 30–81 m). There were 49 (27.7%) recurrences (Colon: 25 and Rectum: 24) and 36 deaths (Colon: 19, Rectum: 14 and other causes: 3). The most common sites of colon relapse were liver and lung and for rectum were local, lung and liver. The univariant analisis of survival shown significance for positive nodes (>3 vs 0 or 1–3) and stage (III vs II) for both Disease Free Survival (DFS) and Overall Survival (OS). Multivariant analisis shown significance for positive nodes (>3 vs 0 or 1–3) and stage (III-II) for (DFS). Only positive nodes (>3 vs 0 or 1–3) shown significance for (OS) Similar survival results were observed for colon and rectum. The modality of treatment did not influenced the clinical evolution of the patiens.

Conclusions: In our study, the association of leucovorin to 5-Fluorouracil-Levamisol did not shown statistical significance of the univariant and multivariant analisis.

246 PUBLICATION

Relationship between s-phase fraction and clinical outcome after surgery for colorectal carcinoma

F. Cianchi[1], M. Balzi[2], A. Becciolini[2], P. Faraoni[2], F. Pucciani[1], G. Perigli[1], P. Bechi[1], A. Palomba[1], G. Ciancio[1], C. Cortesini[1]. [1]Clinica Chirurgica Generale, Università di Firenze, Florence; [2]Laboratorio di Radiobiologia, Università di Firenze, Florence, Italy

Purpose: It has been suggested that cell proliferation characteristics may reflect the biological aggressiveness of colorectal cancer and its prognosis. The aim of this study was to evaluate the relationship between cell proliferation (assessed as flow cytometric S-phase fraction, SPF) and clinical outcome after surgery for colorectal carcinoma.

Methods: This ongoing study has included 148 patients (75 males; 73 females; mean age 63.5 yrs, range 32–75) who underwent radical surgery for colorectal carcinoma by the same surgeon (CC) between 1994–1998. Eighty-eight tumours (59.4%) were located in the colon and 60 (40.6%) in the rectum. Thirty-four tumours (23%) were classified as Dukes A, 75 (50.7%) as Dukes B, 34 (23%) as Dukes C1 and 5 (3.3%) as Dukes C2. Fresh samples of tumour and normal mucosa were analysed using a FACScan Flow cytometer. The analysis of SPF was performed with the Cell Fit Software.

Results: SPF could be evaluated for 134 tumour specimens. The median ± SD of SPF was 16.2 ± 7.1. One hundred and thirteen patients are still living without evidence of disease. Seventeen patients died as a result of tumour relapse. Four patients died of causes not related to the tumour. The median ± SD of SPF was 16.9 ± 7.1 in the living patients and 12.5 ± 7.0 in the patients died of disease.

Conclusion: Our present data showed a trend towards low proliferation rates in patients died as a result of tumour relapse. It is likely that other complex and not completely known factors (such as apoptosis) could affect proliferation of colorectal tumour cells and thus, the prognostic significance of this biological parameter.