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Three drugs schedule in metastatic colorectal cancer (MCC). A phase II study of sequential irinotecan (CPT11), oxaliplatin (l-OHP) plus folinic acid (FA) and short fluorouracil (5FU) infusion

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Oxaliplatin (l-OHP) is a new platinum compound which appears to be active in MCRC with a survival advantage when compared to 5-FU alone. It has demonstrated synergistic activity in combination with various 5-FU-based regimens. Irinotecan (CPT11) is a topoisomerase I inhibitor with antitumor activity in MCC. 5-FU is to date, the cytotoxic agent with the most significant activity in MCC and it represents the base of all chemotherapy schedules for colorectal cancer. The three drugs have an additive/synergistic effect when used them in combination.

Objective: we investigated feasibility, toxicity and response profiles of a 3 drugs combination schedule in unselected pts with MCC to verify if this combination could be more active than single agent schedule.

Methods: from September 2000 to March 2003, 44 consecutive pts (21 females/23 males) received this treatment. Median age was 60 yrs (range 34-80), median ECOG-PS was 0.5 (range 0- 2). Primary tumour site was colon in 40 pts, rectum in 1 pt, unknown in 1 pt and gallbladder in 2 pts. Synchronous metastases were observed in 70% of pts; the metastatic sites consisted in liver (30 pts), lung (12 pts) and peritoneum; 12 pts had 2 or more metastatic organ involvements. 12 pts had prior adjuvant chemotherapy and 2 pts were underwent chemotherapy because of concomitant prostate cancer and SCLC. Comorbidity were hypertension in 6 pts, diabetes in 2 pts, prior myocardial infarction and prior seminomas in 1 pt. The schedule was as follows: CPT11 125 mg/m^2 over 90 minutes plus FA 20 mg/m^2 bolus and 5FU 500 mg/m^2 in 2 hrs infusion on days 1 and 8, L-OHP 85 mg/m^2 over 90 minutes on day 15 and FA 60 mg/m^2 bolus and 5FU 650 mg/m^2 in 2 hrs infusion on days 15 and 16 repeated every 4 weeks. Total number of cycles administered was 196 (media 4,5 - range 1-8).

Results: No toxic therapy-related deaths occurred during the trial. All pts were assessable for toxicity. We observed no grade 4 haematological and non-haematological toxicities, only 3 cases of grade 3 diarrhea and 1 case of grade 3 thrombocytopenia and neutropenia. 5 pts had abdominal pain, 8 pts had paresthesia. Dose reduction was required as follows: by 75% in 13% of cycles, by 50% in 7% of administrations. To date, 36 pts are evaluable for response: we observed 1 CR + 13 PR (38%), 4 MR (11%), 6 SD (16%) according to WHO criteria.

Conclusion: our results suggest that this regimen is feasible and effective, with acceptable toxicity. A longer follow up is needed to confirm these results.

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Preliminary data on weekly irinotecan with continuous oral administration of capecitabine in metastatic colorectal cancer

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Background: Capecitabine (Xeloda®) is a tumor-activated oral fluoropyrimidine, with superior activity and improved safety compared to bolus 5-FU/LV in 1st line MCRC. Addition of irinotecan (CPT) to 5-FU/LV improves efficacy. In combination, infused 5-FU appears to be better tolerated than bolus 5-FU, but infusion is burdensome and time-consuming to patients (pts) and providers alike. Capecitabine (X) mimics continuous infusion 5-FU and could be a safe, effective, and particularly convenient alternative to infused 5-FU in combination with CPT. Continuous dosing of X monotherapy (666 mg/m^2 twice-daily) has been established as safe and effective in MCRC (Van Cutsem, JCO 2000).

Materials and methods: X was administered as a flat dose of 1000 mg twice-daily plus CPT 75 mg/m^2, weekly for the first 4 weeks of each 6-week cycle. Pts $\geq$ 65 years old received a dose reduction of both agents (CPT 60 mg/m^2; capecitabine 750 mg flat dose twice-daily) to improve the combination's safety profile. Objectives were to evaluate efficacy and safety in 1st line MCRC pts.

Results: 38 patients have been enrolled to-date, 37 are evaluable for safety and 28 for response: 27 men (71%), 11 women (29%); median Karnofsky 90 (70-100), median age 64 (39-77). 24 pts (63%) had colon cancer, 10 rectal (26%) and 4 both (10%). Tumor differentiation was 13% poor, 71% moderate, 5% well and 11% unknown. 63% of patients had metastatic disease at initial diagnosis. Most common metastatic sites were liver (79%), lymph nodes (60%), and lung (34%). 11 pts (29%) had received prior adjuvant 5-FU. Mean duration of treatment is currently 89 days (maximum 474; median 52). Most common clinical adverse events (>20% pts) were diarrhea (19% grade 3), nausea/vomiting (11% grade 3) and fatigue (0% grade 3). Overall, 11% of clinical adverse events were grade 3 and 0% grade 4. Incidence of severe toxicity was similar in pts $\geq$ or < 65 (0.5 events/pt vs 0.4). There was no grade 3 Hand-Foot Syndrome or grade 3-4 stomatitis. To-date, there have been 10 PR (36% ORR) of which 3 are yet to be confirmed, with another 5 disease-stabilizations. Updated results will be presented.

Conclusion: These preliminary results suggest that continuous daily oral dosing of X with weekly CPT is feasible and well-tolerated, however the current regimen should be evaluated in the context of other ongoing trials which are evaluating alternative doses and schedules for the combination. In comparison, the 3-weekly regimen using X 1000 mg/m^2 twice-daily d1-14 plus CPT 250 mg/m^2 d1 appears to be highly effective, well-tolerated and particularly convenient (Patt, ASCO 03), and is now moving into phase III evaluation, whilst a 2-weekly schedule is also being developed (Hirawat, ASCO 03).

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Colorectal cancer screening practice in Greece: rates and missed-events.

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Colorectal cancer represents a major public health problem in developed countries: it is the third most frequent cancer in men and women, and it constitutes the third leading cause of cancer mortality. Early diagnositic procedures have been therefore developed to detect colorectal cancer in asymptomatic individuals. Purpose of the study: To index the Hellenic colorectal cancer screening practice (CRCS) and to detect possible barriers to early diagnostic procedures. Considering a possible key role for primary care physicians (PCPh) on CRCS rate, both patients related variables and PCPh screening prescription habitudes were analyzed.

Material and methods: 3000 healthy individuals and 146 PCPh were recruited in 20 Hellenic provinces. The early prevention practice rates of stool occult blood test (SOBT), digital rectal examination (DRE) and total column studies (TCS = sigmoidoscopy, colonoscopy or double contrast barium column studies) were determined and were correlated with sex, age, educational level of the investigated subjects. The screening prescription habitudes of PCPh were further analyzed.

Results: Among individuals aged 50-80, only 2,8% of men and 5,5% of women had an annual SOBT. Within a 10 years period, 6.9% of men and 5.8% of women had a TCS. When Screening SOBT and Screening TCS events were determined and symptomatic individuals who performed the examinations were excluded, the screening practice rates dropped to 1,6% both for SOBT and TCS, and for both sexes. DRE screening rates in females was similar to SOBT and TCS. Among men annual DRE rates were higher in the elderly (19% in age 70-80). However, in this population Screening DRE was performed in 4% of asymptomatic individuals. The observed SOBT, DRE, TCS Screening rates were not influenced by sex, age and educational level of the investigated individuals. Among PCPh, 45%, 37%, and 68% did not recognize any significant role for SOBT, DRE and TCS for the early diagnosis of colorectal cancer.

Conclusions: Colorectal cancer screening practice was found to be inconsistent among the evaluated individuals. The role of PCPh has to be strengthened. Continual medical education in screening practice seems to be required for medical personnel employed in PCPh activities.