255 PUBLICATION

The peculiarity HLA-allels and HLA-lymphocyte phenotypes in the patients of Uzbek population suffering from colorectal cancer

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Introduction: The purpose of our study was the determination of peculiarity HLA-allels and HLA-lymphocyte phenotypes in the patients (pts) of Uzbek population (Uz.p) suffering from colorectal cancer (CC).

Methods: 77 pts with CC were studied. The HLA-typing class I was performed by routine lymphotoxic test with complement. The monospecific anti HLA-globulins were used.

Results: Study of distribution of HLA class I revealed reliable increased frequencies of HLA A28; B27; B8; B40 allels (p 0.05). Also were defined high level of predominance the unprofitable HLA-lymphocyte phenotypes, which was characteristic for many pts 96.1%. Three basic types of unprofitable HLA limphocyte phenotypes has been defined: I – total absence one or two HLA locuses 32.45%; II – absence some HLA-A; -B; -C allels 15.5; III-total absence of HLA locus and loose one of allels from other locuses. Only 3 pts had "full house" HLA-phenotypes 3.9%.

Concusion: The people with A28; B27; B8; B40 HLA allels are group of risk to the CC in Uz.p. The loss of capability for expression HLA-molecules in the immunocompetent cells may be also one of primary pathogenetic parts in the development of cancer diseases.

256 PUBLICATION

Oxaliplatin (L-OHP) in combination with leucovorin and bolus-continuous infusion 5fluorouracil (LV5FU2) in advanced colorectal cancer (ACC) pretreated with 5fu

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L-OHP is active against ACC both in 1st and 2nd line; in 1st line the combination with LV5FU2 demonstrated an increased activity in comparison to LV5FU2 alone (De Gramont, ASCO 1998). We performed a phase II trial in order to evaluate the activity of L-OHP + LV5FU2 in patients (pts) pretreated with 5FU.

From 4/96 to 3/99, 55 pts (34 male, 21 female; mean age 59.5 years; PS 0:22, 1:21, 2+ 3:12; liver mts: 38) with ACC progressing after 5FU-based chemotherapy entered this trial: in 24, 1st line treatment was bolus 5FU (modulated by LV or MTX or IFN) and in 31, infusional 5FU (LV5FU2 in 21, other regimens in 10). In 23 pts a 2nd or 3rd line therapy had been administered before entering the study. The treatment schedule was: L-OHP 85 mg/sqm every 2 weeks + 2 h 1-LV 100 mg/sqm and 5FU 400 mg/sqm bolus followed by 600 mg/sqm in 22 h infusion on day 1 and 2 every 2 weeks. In the 41 pts up to now evaluable (14 are early) we observed: 0 CR, 13 PR, 14 NC (with a tumor growth control in 66%) and 14 PD. The median time to progression was 5+ months and overall survival 7 months. Side effects were: peripheric neuropathy (grade 1–2: 25%, grade 3–4: 3.6%) and moderate myelotoxicity, mucositis and diarrhoea.

This treatment is active in 5FU pretreated pts and should be evaluated in comparison to CPT-11 ± continuous infusion 5FU.

257 PUBLICATION

Oxaliplatin, 5-FU and folinic acid (OFFA) as II-line chemotherapy in advanced colorectal cancer

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Introduction: We report our experience with OFFA as II line chemotherapy in advanced colorectal cancer.

Methods: 26 consecutive pre-treated patients with advanced colorectal cancer were treated with oxaliplatin 130 mg/m^2 day 1°, 5-FU 375 mg/m^2 day 1°–>5°, folinic acid 20 mg/m^2 day 1°–>5°, every 28 days. All patients presented a progression of disease after I-line 5-FU-based chemotherapy, and an evaluable disease. Every two courses of chemotherapy, a restaging of disease was performed, and the treatment was discontinued for progression of disease or toxicity.

Results: Till today, 97 courses of chemotherapy have been performed in the 26 enrolled patients, with a median courses/patient ratio of 4 (range 1–8). All patients are evaluable for toxiciy, and 22 ones for response. We observed 1 partial response (3.8%), 9 stabilizations of disease (34.6%) and 12 progressions of disease (46.2%) with a time to progression of 71 days. Till today 12 patients are dead, with a time to survival approximatively of 10 months. No grade III–IV hematologic toxicity was observed, grade III diarrea and grade III mucositis were observed respectively in 2 (7.4%) and 1 (3.8%) patients, with no other grade III non-hematologic toxicities. Grade II and grade I neurologic toxicity were observed respectively in 8 (30.8%) and 9 (34.6%) patients.

Conclusions: OFFA represents an effective and well tolerated option when a progression of disease after 5-FU-based regimens occurs: our data could also suggest the use of OFFA as I-line chemotherapy besides as II-line one for advanced colorectal cancer. Supported by Istituto Oncologico Romagnolo IOR.

258 PUBLICATION

'Tomudex' (raltitrexed) has a manageable toxicity profile in elderly patients with metastatic colorectal cancer

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Introduction: 'Tomudex' is an effective alternative to 5FU as monotherapy in the treatment of adult patients with advanced colorectal cancer. A multicentre Phase II study was therefore conducted principally to assess whether the safety profile of 'Tomudex' extends to elderly patients in this setting.

Methods: Elderly patients aged >/=70 yrs with previously untreated or adjuvant treated advanced colorectal cancer were eligible for inclusion. 'Tomudex' 3 mg/m[2]/day was given by 15-min iv infusion every 3 weeks until disease progression or significant toxicity. Tolerability was principally assessed by monitoring the frequency of serious (WHO grade III/IV) adverse events.

Results: 51 patients (34 male, 17 female) with a median age of 75 yrs (range 70–89 yrs), and a WHO performance status of 0 (24 pts), 1 (20 pts), or 2 (7 pts) were included. 35 pts with colon cancer and 16 with rectal cancer had metastases at 1 (40 pts) or 2 (11 pts) sites located in the liver (33 pts), lung (10 pts), peritoneum (9 pts), bone (3 pts) or at other sites (7 pts). 14 pts had previously received adjuvant chemotherapy. 205 cycles (median 4, range 1–13) giving a median relative dose intensity of 95% (range 44–103%) have been delivered. Grade III–IV toxicities were seen in 24 pts (47%). Grade III/IV anaemia was seen in a total of 9 treatment cycles (6 pts, 12%), neutropenia in 2 cycles (2 pts, 4%), and thrombocytopenia in 1 cycle (1 pt required platelet transfusion, 2%). Other grade III/IV toxicites were: nausea/vomiting, 9 cycles (7 pts, 14%); diarrhoea, 6 cycles (5 pts, 10%); infectious disease, 6 cycles (5 pts, 10%); asymptomatic increase in transaminase activity, 13 cycles (12 pts, 24%). 10 pts (20%) experienced severe asthenia (12 cycles). There have been no toxic deaths. Among 35 pts evaluable for efficacy there have been 1 confirmed complete response and 8 partial responses (RR 26%). 14 pts (40%) experienced stable disease.

Conclusions: These preliminary results suggest that 'Tomudex' has a manageable toxicity profile in elderly patients with untreated metastatic colorectal cancer.

'Tomudex' is a trade mark, the property of Zeneca Ltd.

259 PUBLICATION

Preoperative radiotherapy for advanced lower rectal cancer-combination of external and high-dose-rate intraluminal radiotherapy

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Purpose: To evaluate the therapeutic results of preoperative irradiation using a combination of external irradiation and high-dose-rate intraluminal irradiation using 60Co (RALS) aimed at enhancing postoperative local control of advanced lower rectal cancer.

Methods: The subjects comprised 38 patients (31 men and 7 women) in whom "∫T3 lower rectal cancer was suspected and who underwent preoperative irradiation (RT group). A control group (N-RT group) consisted of 19 patients subjected to operation alone in whom postoperative histolog-

ical study revealed ^{ac}pT3 lower rectal cancer. The external irradiation was performed with a 10MVX delivering 30–40 Gy/15–20 Fr to the entire pelvic cavity. RALS was performed 30–40 Gy/3–4 Fr (dose evaluation point set at 1.0 or 1.5 cm from the source). After a mean waiting period of 14 days after irradiation, abdomino-perineal resection (APR) was performed in 34 cases and low anterior resection (LAR) in four. In the N-RT group, the surgical procedure was APR in 13 cases and LAR in six.

Results: Five and 8-year survival rates were 83 and 83% in the RT group, and were 80 and 80% in the N-RT group. The local recurrence rate was 5% in the RT group in contrast to 21% in the N-RT group.

Conclusion: Although a significant enhancement of the survival rate was not achieved by preoperative radiotherapy with external plus intraluminal irradiation for advanced lower rectal cancer, this treatment contributed to excellent local control and a decrease in the local recurrence rate.

260 PUBLICATION

A phase II study of alternating cycles of CPT-11 and high-dose 48 hour infusion 5-FU in combination with leucovorin (HD-5-FU/LV) in no selective patients with metastatic colorectal cancer (MCRC)

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Purpose: A weekly 48 hour infusion of HD-5-FU/LV and CPT-11 are effective in the treatment of the MCRC. Even if CPT-11 seems to have incomplete cross-resistance with 5-FU, pharmacodynamics data recommend caution in evaluating their combination. For this reason we performed a trial in which CPT-11 and HD5-FU/LV were administered on alternating cycles.

Methods: No selective 20 pts with MCRC received 5-FU 2600 mg/m^2 over 48 hrs q wk × 4 in combination with LV 150 mg/m^2 followed by a 2-week rest, and then CPT-11 350 mg/m^2 q 3 wks. Median age = 68 (45–79); PS (WHO): 0/1/2, 3/15/2. Most frequent metastatic sites were liver 12 (60%) and lung 6 (30%). 5/20 pts were pretreated for metastatic disease and "bulky" disease was diagnosed in 8 cases before treatment.

Results: All patients were evaluable for toxicity and 18 for response. 2 pts achieved, a CR and 2 pts achieved a PR for an overall response rate of 22%. 12 pts (66%) reported a stable disease. An assessment of median time to tumor progression and survival are in progress. The incidence of grade 3–4 toxicity for patient in any cycle is for CPT-11: diarrhea 10%, naus/vom 10%, neutropenia 15%; for HD-5FU/LV: diarrhea 5%, naus/vom 5%, stomatitis 15%.

Conclusion: An alternating regimen of CPT-11 and HD-5-FU/LV is active even if the preliminary response rate is not clearly different than that of either CPT-11 or HD-5-FU/LV alone. Therefore, the high percentage of stable disease, the unfavourable characteristics of pts and the low toxicities stimulate us to continue our study.

261 PUBLICATION

Phase-II-study of a 24-h infusion with 5-fluorouracil (5-FU) and simultaneous sodium-folinic acid in the first-line-treatment of advanced colorectal cancer: Interim analysis

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Introduction: Weekly continuous high dose therapy with 5-FU and Calcium-folinic acid (Ca-FA) according to "Ardalan" has shown to be an effective treatment in advanced metastatic colorectal cancer. Sodium-folinic acid (S-FA) is a new formulation, which in contrast to Ca-FA allows the simultaneous iv-administration in one pump. Thus, the effect of both drugs might be augmented due to improved 24 h-kinetics. Purpose of this study was to evaluate effect and toxicity of this new combination.

Methods: Since 1997 50 patients with metastatic colorectal cancer have been recruited to receive weekly 24 h-infusions of 5-FU (2600 mg/m^2) and S-FA (500 mg/m^2) combined in one pump for 6 weeks. Treatment was repeated after a 2-week rest period.

Results: 28 patients having either received at least 2 courses of chemotherapy or showing early progression up to now are evaluable for response according to study protocol. Their median follow up is 8 months. Of these the response rate for CR and PR was 50% (14/28) with 1 CR (3.6%), 13 PR (46.4%), 11 NC (39.3%) and 3 PD (10.7%). The worst toxicities experienced by 43 evaluated patients (106 treatment courses) were gastrointestinal side effects. Grade IV diarrhea appeared in 3.8%, grade IV stomatitis in 0.9% of the treatment courses. Grade III hand-foot-syndrom was seen in 3.8%, grade III diarrhea in 7.5% und grade III stomatitis in 2.8%. Treatment was stopped in one patient due to cardiac toxicity after the third administration in the first course.

Conclusion: The early data in this study indicate a potentially augmented effectiveness for weekly simultaneous 24 h-infusion therapy with 5-FU and S-FA in metastatic colorectal cancer. Treatment is feasible with respect to toxicity.

262 PUBLICATION

The distribution of polymorphic enzymes in colon cancer case

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Purpose: The polymorphic enzymes N-acetyltransferase (NAT2), glutathiontransferase M1 (GSTM1), and T1 (GSTT1) are predisposing factors for several human cancers. Colon cancer is associated with genetic, occupational, and enviromental factors. Therefore, several studies for genotyping this enzymes were performed on colorectal cancer cases. Most of these studies revealed an overrepresentation of the rapid acetylator status.

Methods: The distribution of NAT2, GSTM1, and GSTT1 was investigated in 80 colon cancer cases and 140 controls (suffering from non-malignant diseases) in a case-control study. They were genotyped from leucocyte DNA by PCR and RFLP. Additionally, possible occupational and non-occupational exposures to carcinogens were investigated using a questionnaire.

Results: In the cancer cases 65% were "slow" acetylators, 53% were GSTM1 negative and 15% were GSTT1 negative. In controls 61% were "slow" acetylators, 51% were GSTM1 negative and 14% were GSTT1 negative. The results presented are in line with the assumption, that the enzym status of the polymorphic enzymes NAT2, GSTM1 and GSTT1 cannot be seen as a general genetically determined risk factor for colon cancer.

Conclusion: The impact of occupational and/or environmental factors in an industrialized area with a known elevated colon cancer mortality might be considered as possible cause for the ordinary distribution of the "slow" NAT2 genotype in the cases investigated.

263 PUBLICATION

Oxaliplatin (OX) after irinotecan (IRI): Antitumour activity and clinical benefit of 3rd and higher line chemotherapy with ox for patients (pts) with metastatic colorectal cancer (MCC) after failure of IRI

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Purpose: There is no data concerning the use of chemotherapy (CT) alter failure of IRI, an agent that is active in 2nd-line CT for MCC.

Methods: All pts in eight german centers who received an OX-containing regimen after they had been treated with IRI (350 mg/sqm q3w) as 2nd -or higher-line and progressive disease (PD) occurred were analysed for best response (BR) to IRI to OX and for subjective response rate (SRR) or clinical benefit in pts with tumour related symptoms (TRS).

Results: Out of 34 identified pts all but 4 showed PD while receiving IRI or within 6 weeks after last IRI. In 17 pts PD was BR to IRI defined as primary resistance (IRIPRIRE). 11 pts were treated with single agent OX (130 mg/sqm q3w) while in 23 cases different combination regimens with OX and folinic acid and high dose infusional 5-Fluorouracil (OX-HDFAFU) in full dose was administered. OX was 3rd-line in 23 pts and higher line in 11 pts.

Efficacy: PR. 4 pts (ITT 12%), MR or NC: 15 pts (tumour control rate 56%), PD: 3 pts, not evaluable 3 pts. TTP from start of OX was 1 to 17 months (m), median 3 m. 18 pts suffered from TRS that improved in 8 while receiving OX (SRR 44%). ORR and SRR were poorer in pts treated with single agent Ox. IRIPRIRE: Out of 17 pts 3 achieved a PR and 8 NC (median TTP and SRR comparable to whole group).

Conclusion: Our analysis indicate that OX-HDFAFU might be considered in pts with MCC progressing under IRI and underline the lack of cross resistance of the two regimens in a clinical setting.