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'Tomudex' (raltitrexed) 4.0 mg/m[2] as second- or third-line therapy in patients with advanced colorectal cancer: A Phase II study

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Objectives: 'Tomudex' (raltitrexed) has comparable efficacy to 5FU when used first-line in patients (pts) with advanced colorectal cancer (aCRC), and at the recommended dose of 3 mg/m[2] it is often perceived to have a generally mild toxicity profile. This study investigated the efficacy and tolerability of 'Tomudex' 4.0 mg/m[2] as second- or third-line therapy for aCRC pts.

Methods: Pts were eligible if aged >/=18 yrs with metastatic, locally recurrent or unresectable colorectal cancer that had been unsuccessfully treated with bolus 5FU first-line therapy or irinotecan second-line therapy. Efficacy assessments included objective response and survival; tolerability was assessed by monitoring clinical/laboratory findings and adverse events.

Results: To date, 21 pts are evaluable for toxicity. 9 pts have experienced 24 grade III or IV adverse events (AEs), of which 4 were hematologic (thrombocytopenia [n = 2], neutropenia [n = 1] and anemia [n = 1]). The only AEs occurring in >1 pt were: elevated alkaline phosphatase (n = 2); sepsis (n = 3); thrombocytopenia (n = 2); and dehydration (n = 2). None required dose reduction. 3 pts were hospitalized with AEs considered related to treatment: 1 pt with shortness of breath and nausea/vomiting, and 2 pts with sepsis (1 was withdrawn). There have been no toxic deaths. Detailed safety and efficacy data are currently being evaluated.

Conclusions: These preliminary data indicate that 'Tomudex' 4.0 mg/m[2] has an acceptable tolerability profile: in patients with aCRC whose disease had progressed on prior first-line 5FU-based treatment or second-line irinotecan treatment. Efficacy results are awaited with interest.

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Second line treatment with irinotecan (CPT11) in patients (pts) with advanced colo-rectal carcinoma (ACRC) resistant to 5FU

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Objective: To evaluate efficacy and toxicity of CPT11 in pts with advanced colo-rectal carcinoma resistant to 5FU based schemes.

Methods: From January 97 to December 98, 42 pts with progressive ACRC after 5FU chemotherapy were treated. CPT11 350 mg/2 was given in 90 minutes, iv, premedicated with atropine, every 21 days until progressive disease or unacceptable toxicity. Mean age: 58.7 y (range 31–74). Males: 32 (76%), females 10 (24%). Colon 23 (55%), rectum 19 (45%). One site affected: 24 (57%) (liver in 9 cases), two or more: 18 (43%) (liver and peritoneum in 7 cases). High doses of Loperamide and/or Ciprofloxacin were given if late diarrea.

Results: Evaluable for response: 31 (74%) pts (5 early death, 6 less than 3 cycles), with 2 complete response (6%), 5 partial response (16%), 12 stable disease (39%) and 12 progression (39%). Of the 19 pts with response or stable disease, 8 have progressed, with a free of progression time of 21.8 weeks (range 4.2–39.4), and eleven have not progressed yet. Evaluable for toxicity: 37 (93.7%) pts. 179 cycles, mean 4.26 cycles/pt (1–14). Haematological toxicity grade (g) III: 3 cycles (1.6%), gIV: 2 cycles (1.1%). Two episodes of febrile neutropenia. Non-haematological toxicity: Emesis gIII: 7 cycles (3.9%), diarrhea gIII: 9 cycles (5%), asthaenia gIII: 5 cycles (2.7%). There was no toxic deaths. Overall survival rate (Kaplan-Meier) 34% at 1 year. Median survival time was 10.5 months for the entire population.

Conclusion: CPT11 is an active treatment in patients with ACRC resistant to 5FU based schemes, with controlable toxicity used in an out-patient basis. It has a good therapeutic index and represent a new treatment option for these patients.

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A phase II trial of pre-operative radiation therapy with concomitant 5-FU and sphincter-sparing surgery (preliminary results)

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Purpose: A prospective phase II trial was initiated at the Dept. of Radiation Oncology in cooperation with Dept. of Surgery on patients with rectum cancer which were initially inoperable or not suitable for sphincter-sparing surgery to assess acute toxicity and feasibility of the combination of preoperative external beam radiation therapy and sphincter-sparing surgery.

Methods: Patients were evaluated and staged by joint team of surgeons and radiation therapists using the clinical staging system proposed by Mohiuddin et al. Eligible patients were irradiated using four field "box" technique (primary tumour and locoregional lymph nodes) with 1.8 Gy per fraction 5 days a week administering 45 Gy. 5-FU was administered concomitantly 250–300 mg/m^2 thrice weekly. Patients were re-evaluated by the same joint team to assess the downstaging of the tumour and eligibility for the sphincter-sparing surgery at the last day of initial phase of the treatment. Patients with insufficient downstaging were continued to be irradiated using same treatment portals and fractionation to a dose of 50.4 Gy. A second re-evaluation was done by the same joint team and ineligible patients were continued to be irradiated using reduced AP-PA "boost" fields (primary and involved nodes; only) to a dose of 54 Gy with 1.8 Gy per fraction. Last preoperative re-evaluation was performed and still ineligible patients were considered for the full-dose radiation therapy program with or without concomitant chemotherapy.

Results: As of March 1999, 21 patients were evaluated (median follow-up of 17 months with a range of 3–34 months). No Grade 3 and 4 acute toxicity was observed. In 12 patients (57%), sufficient downstaging was achieved and 6 of them (28%) had sphincter-sparing surgery. Nine patients were evaluated as stable disease (43%). Eleven patients had abdominoperineal resection (52%). Four patient (21%) has been transferred to full-dose radiation therapy program because of insufficient response.

Conclusion: Toxicity was well-tolerated and no treatment-related death occurred with combined pre-operative concomitant chemoradiotherapy regimen and sphincter-sparing surgery. Although it appears that this regimen can increase the rate of downstaging and surgical eligibility, additional phase II/III studies are needed.

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'Tomudex' (raltitrexed) plus oxaliplatin (Eloxatin) in previously untreated metastatic colorectal cancer (MCRC) patients: An active combination

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Objectives: This Phase II study was initiated to evaluate a combination of 'Tomudex' (raltitrexed) and oxaliplatin (Eloxatin), both active as single agents, in MCRC pts previously untreated with chemotherapy for advanced disease.

Methods/Results: Pts were administered 'Tomudex' 3 mg/m^2 (15-min iv infusion) and, 45 min later, oxaliplatin 130 mg/m^2 (2-h iv infusion), every 3 weeks. 40 pts were evaluable (27 M/13 F; median age 63 [39–75] yrs; WHO PS 0 [23 pts] or 1 [17 pts]; 28/12 colon/rectal cancer; Dukes' stage B [2 pts], C [10 pts], D [28 pts]). Toxicity included grade III/IV neutropenia (6 pts), thrombocytopenia (2 pts), diarrhoea (3 pts), nausea/vomiting (2 pts), mucositis (1 pt), increased transaminase activity (4 pts), and grade I or II peripheral neuropathy (2 pts). 1 toxic death was seen after cycle 3 (grade IV diarrhoea and neutropenia). 27 pts had a PR (RR = 67.5% [95% CI 50.9–81.4%]), SD = 9 pts (22.5%) and PD = 4 pts (10%). Median response duration and TTP are both ≥4 months.

Conclusion: The 'Tomudex' plus oxaliplatin combination is active in untreated MCRC patients and has an acceptable toxicity profile. Updated results from the whole 71-pt cohort will be available in September 1999.

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