Conclusions: These studies show that peritoneal carcinomatosis can be treated with curative intent. Selection of patients is of utmost importance in these patients requiring aggressive and expensive interventions. Treating carcinomatosis concomitantly with the primary cancer showed benefit with minimal additional morbidity and mortality.

230 PUBLICATION

The prognostic significance of elevated serum CA19-9 level in patients with metastatic colorectal cancer

A. Wong, A.K.P. Chan. *Tom Baker Cancer Centre and University of Calgary, Calgary, Canada*

Purpose: This study was undertaken to evaluate the prognostic influence of serum CA19-9 level on the survival of patients with metastatic colorectal cancer.

Methods: Serum tumour markers CA19-9, CEA and five other major clinical parameter were prospectively collected for 238 patients at time of diagnosis of unresectable metastatic colorectal cancer. The Cox Proportional Hazard Model was used for multivariate analysis to evaluate the prognostic significance of CA19-9, CEA, LDH, alkaline phosphates, tumour differentiation, ECOG performance status, chemotherapy treatment (leucovorin/5FU) on survival time of patients.

Results: In multivariate analysis, an elevated CA19-9, poorly differentiated tumour histology, poor ECOG performance and absence of chemotherapy treatment were independently adverse prognostic indicators for survival For 101 patients with CA19-9 less than 35 at diagnosis of unresectable metastases, the median survival was 23 months as compared to a median survival of 9 months for another 137 patients with CA19-9 greater than 35 ($p = 0.0011$).

Conclusion: Clinical trials in metastatic colorectal cancer should include CA19-9 as one of the pre-treatment prognostic factors.

231 PUBLICATION

Screening for HNPCC-focussing on families

S. Sahm[1], J. Raedle[2], A. Schmied[2], W. Caspary[2], S. Zeuzem[2]. [1]*Deutsche Klinik für Diagnostik, gastroenterology, Wiesbaden;* [2]*University of Frankfurt, medical clinic II, Frankfurt, Germany*

HNPCC accounts for about 5% of all colorectal cancers (CRC). HNPCC families are characterised by an increased incidence of extraintestinal cancers as well. Conventional screening stategies focus on patients with CRC. We tried to establish a screening program focussing on families.

Methods: Standardized interview including familial pedigree of patients undergoing colonoscopy in a medical referral center. Malignancies within the families were documented and criteria associated with an increase of familal clusters (>3, Clu+) of HNPCC like tumors (tC) were looked for. (fisher's test).

Results: 463 screened, 1/463 fulfilled Amsterdam criteria, 6/463 Bethesda criteria, 71 showed clusters. The presence of one person within a family diagnosed with cancer at an age < 55 yrs (age+) was closely associated with Clu+: 86/463 age+, 39 (8.4%) of whom cluster + ($p = >0.0001$, fisher's test).

Conclusion: 1) Standard criteria fail to identify families with clusters of tC. 2) Diagnosis of a tC at an age < 55 yrs is strongly associated with Clusters of tC within a family suggesting screening for HNPCC.

232 PUBLICATION

'Tomudex' (raltitrexed) plus 5FU combination treatment for patients with advanced colorectal cancer: A Phase I study

S. Mayer[1], R. Hilger[1], C. Muller[1], D. Dohmen[1], R. Kloeppel[2], U. Vanhoefer[1], M.E. Scheulen[1], S. Seeber[1], A. Harstick[1]. [1]*West German Cancer Centre, Essen;* [2]*Zeneca GmbH, Germany*

Objectives: 'Tomudex' (raltitrexed) and 5FU both have clinical activity as single agents in the treatment of advanced colorectal cancer, and preclinical studies have demonstrated a schedule-dependent synergism between these agents, with high antitumour activity when 'Tomudex' is administered prior to 5FU. Therefore, a Phase I trial of 'Tomudex' combined with 5FU was initiated in patients with metastatic colorectal cancer.

Methods: 5FU (24-h infusion) was administered weekly at the following dose levels (mg/m[2]): 1200 (level 1), 1600 (level 2), 2000 (level 3), 2400 (levels 4 and 5), 2800 (level 6) and 2600 (level 7). 'Tomudex' (15-min infusion) was administered on days 8 and 29, 15-min prior to 5FU, at a dose of 2.6 mg/m[2] (levels 1–4 and 7), or 3.0 mg/m[2] (levels 5 and 6). Each cycle consisted of 5 weeks' treatment followed by 1 weeks' rest. Pharmacokinetics of 5FU were obtained at week 1 (without 'Tomudex') and week 2 (after 'Tomudex') in cycle 1.

Results: To date, 35 patients have been entered and have received a total of 82 cycles of treatment. No DLT occurred at dose levels 1–4. At dose level 5 ('Tomudex' 3.0 mg/m[2]; 5FU 2400 mg/m[2]), 2/3 female patients had DLT (grade III diarrhoea and thrombocytopenia, and grade, IV leucopenia and thrombocytopenia; the latter died of lethal septicaemia in week 6), whereas, the 3 male patients had no DLT. No DLTs were experienced by the 6 male patients entered at dose level 6, although 4 withdrew due to nonDLT events. 6 patients (5 F/1 M) entered at dose level 7 are not yet evaluable. Coadministration of 'Tomudex' resulted in a significantly increased 5FU C[max] and AUC in week 2 compared with week 1 ($p = 0.007$ and 0.03 respectively; 2–6 patient samples analysed per dose level). Of 16 patients on dose levels 3–6 evaluable for response, 9 (56%) have achieved a partial response.

Conclusions: The likely recommended dose is 2.6 mg/m[2] for 'Tomudex' and 2600 mg/m[2] for 5FU. This regimen of 'Tomudex' and 5FU demonstrated promising activity and manageable toxicity and will be evaluated in a Phase II trial.

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233 PUBLICATION

'Tomudex' (raltitrexed) plus 5-fluorouracil: A promising option for the treatment of patients with metastatic colorectal cancer

G.K. Schwartz[1], J. Bertino[1], N. Kemeny[1], L. Saltz[1], D.K. Kelsen[1], W. Tong[1], J. Barazzuol[1], C. Lowery[2], M. Smith[3]. [1]*Memorial Sloan-Kettering Cancer Center, New York;* [2]*Zeneca Pharmaceuticals, Wilmington, DE, United States;* [3]*Zeneca Pharmaceuticals, Alderley Park, United Kingdom*

Objectives: 'Tomudex' (raltitrexed) is a specific inhibitor of thymidylate synthase with activity in advanced colorectal cancer. Synergy has been demonstrated in cancer cell lines when 'Tomudex' is followed 24 h later by 5FU. Therefore, in this Phase I dose-escalation study, patients with metastatic disease, who had failed 5FU or CPT-11, were administered 'Tomudex' followed 24 h later by 5FU (bolus injection), once every 3 weeks.

'Tomudex'/5FU dose (mg/m^2)	OR n	SD n	PD n	DLT n	Mean 5FU AUC (SD) (μM/min)
0.5/900	1PR[a] 1	1	0	10498 (1119)	
1.0/900	0	2	1	0	9176 (611)
1.5/900	0	2	1	0	5362 (2591)
2.0/900	1PR[a]	1	1	0	6794 (1167)
2.5/900	0	3	0	0	19593 (6074)
3.0/900	1CR	0	2	0	16360 (1452)
3.0/1050	0	1	2	0	20979 (6046)
3.0/1200	1MR[a]	1	2	0	20770 (5178)
3.0/1350	1PR[a]	2.	1	3 – nadir fever	20377 (1063)
3.5/1200	0	1	2	0	22801 (8269)
4.0/1200	0	2	3	1 – nadir fever	16880 (3628)
4.5/1200	0	2	1	0	20748 (7539)
5.0/1200[b]	0	2	1	1 – neutropenic fever	NA
Total	5	20	18		

[a]pt previously failed 5FU therapy; [b] 3 pts not yet evaluable for response

Methods/Results: No pt had a DLT at doses ≤3.0/900 mg/m^2; therefore the 5FU dose was increased. At 3.0/1350 mg/m^2, 3/4 pts experienced DLT; the 5FU dose was therefore maintained at 1200 mg/m^2 while the 'Tomudex' dose was escalated. The combination had a manageable toxicity profile, the most common toxicity being short-lived, non-dose-limiting neutropenia (without fever). 5/43 (12%) pts had an OR and 20/43 (47%) had SD. The median survival was 14.3 months (95% CI 11.7, 21.9). 'Tomudex' increased the AUC of 5FU at doses >2.5 mg/m^2.

Conclusions: The median survival in this preliminary study compares favorably with other second-line regimens, including CPT-11 (9.5 months) and oxaliplatin/5FU (7–17 months). These results suggest that this 'Tomudex'/5FU combination has a manageable toxicity profile, and is a potential attractive option for improving palliation and survival in heavily pre-treated pts.

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