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Economic evaluation of capecitabine (X) vs. bolus 5-FU/LV as adjuvant chemotherapy for patients (pts) with Dukes' C colon cancer in an Italian hospital setting

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Background: In the primary analysis of the recent X-ACT adjuvant trial, X showed consistent benefits over bolus 5-FU/LV, with at least equivalent disease-free survival (DFS), and an improved safety profile [Cassidy et al. 2004]. In addition, X demonstrated superior relapse-free survival (65.5% vs. 61.9% at 3 years follow-up; p = 0.0407) and improved covariate-adjusted overall survival (p = 0.0208). In order to determine the potential economic impact of X in this setting, we used the results from X-ACT to assess the cost-effectiveness of X from the Italian hospital perspective.
Materials and methods: Trial-based data were collected on treatment period medical resource use. Unit costs for drug administration, hospitalisations, emergency room visits, and concomitant medications were considered using published sources in Italy. A health-state transition model was used to estimate incremental cost impact and the effectiveness in terms of the gains in quality-adjusted life months (QALMs). Costs and effectiveness were discounted at 3.5%.
Results: Mean duration of treatment was similar with X and 5-FU/LV, and pts received 92% and 93% of planned treatments, respectively. Administration of X required fewer clinic visits per pt (7.4 versus 28.0 with 5-FU/LV). Acquisition costs of X were higher than 5-FU/LV, approximately 2533 vs. 231 Euros, but this difference was more than fully offset by the difference in administration cost of 5-FU/LV (4338 vs. 152 Euros for X). Total hospital days for treatment-related adverse events (AEs) and medication costs for treating AEs were higher for 5-FU/LV than X. The cost of emergency room visits for treating AEs did not differ. Compared with 5-FU/LV, X is projected to increase QALMs by 6.5 months, with overall treatment period cost savings of 2234 Euros. These findings show that X is a dominant (cost-saving and more effective) treatment in this setting. Similar findings were reported from a similar analysis in UK patients [Douillard et al. 2004].
Conclusions: X as adjuvant treatment for pts with colon cancer is not only clinically effective with an improved safety profile vs. 5-FU/LV, but it is also a dominant choice from an economic perspective.

676 PUBLICATION

Comparison between endorectal ultrasonography and magnetic resonance imaging in preoperative staging of rectal cancer

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Background: Preoperative staging of rectal cancer is essential for optimal therapy planning. The aim of this study was to evaluate the accuracy and clinical usefulness of endorectal ultrasonography (ERUS) and magnetic resonance imaging (MRI) in preoperative staging of rectal cancer.
Materials and methods: Between May 2003 and February 2005, 35 patients with histologically proven rectal cancer were examined with endorectal ultrasonography using 5.0–7.5 MHz endorectal probe and MR imaging (1.5 T) using a whole-body coil.
We compared results of ERUS and MRI staging with the pathology findings based on the surgical specimens.
Results: The overall accuracy of ERUS for determining depth of invasion (T stage) was 74% (26/35) and 71.4% (25/35) for MRI. Overstaging was 5.7% (2/35) by ERUS and 8.6% (3/35) by MRI. Both ERUS and MRI understaged 20% (7/35) of patients. In staging perirectal lymph node metastasis. the overall accuracy rate of ERUS was 68.5% (24/35) with 14.3% (5/35) overstaged and 17% (6/35) understaged. MRI correctly identified the N stage with an accuracy rate of 65.7% (23/35); 20% (7/35) of patients were overstaged and 14.3% (5/35) understaged.
Regarding penetration of the rectal wall (stages T1 and T2 vs stages T3 and T4). ERUS and MRI showed identical sensitivity of 72% and specificity of 90%. With regard to nodal involvement. sensitivity was 62.5 and specificity 78.9% for ERUS and 68.7% and 68.4% for MRI.
Conclusions: Both ERUS and MRI are reliable diagnostic modalities in staging rectal cancer with similar accuracy. ERUS is fast, safe and more cost-effective than MRI and therefore should be prefered while MRI has its role when ERUS is not feasibile (in stenotic and proximal rectal cancers) and in cases of advanced disease.

677 PUBLICATION

Tolerability of yttrium-90 chemoradiation treatment of liver metastases from colorectal cancer: international clinical trial

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Background: Liver metastases are detected in over 70% of patients with advanced colorectal cancer and represent the principal cause of death in this patient population. Surgical resection of hepatic disease may improve survival, but this strategy is not feasible in the majority of patients with metastatic disease. Selective internal radiation therapy (SIRT) involves the injection of SIR-Spheres® (which contain the beta-emitter, yttrium-90) into the arterial supply of the liver resulting in preferential lodgement in malignant microvasculature, delivering approximately 200 Gy to tumour tissue. In a Phase 2 feasibility trial, the combination of SIRT with systemic 5-fluorouracil (5-FU) and folinic acid (LV) improved median survival by 16 months compared to systemic chemotherapy alone (van Hazel et al. J Surg Oncol 2004; 88: 78–85). Oxaliplatin is a radiosensitising diaminocyclohexane-platinum compound. Th ombination of 5-FU/LV and oxaliplatin (FOLFOX4) appears synergistic in the treatment of advanced colorectal cancer. We tested the hypothesis that FOLFOX4 with concomitant SIRT is well tolerated.
Methods: A 2-centre Phase I study of Sir-spheres® with modified FOLFOX4 systemic chemotherapy was conducted in patients with inoperable liver metastases from colorectal carcinoma who had not received prior chemotherapy for metastatic disease. In the context of full-dose 5-FU and LV, inter- and intra-patient dose escalation was performed with oxaliplatin (30 to 85 mg/m^2). SIRT was administered on day 3 or 4 of the first cycle of chemotherapy. The primary endpoint was toxicity.
Results: Seventeen patients were entered into the study. The mean dose of SIRT administered was 1.7 GBq (range 0.9 to 3.1 GBq). Six patients received 85 mg/m^2 of oxaliplatin from cycle 1. Of the 169 cycles administered, the total dose delivered was 91% of the protocol chemotherapy dose. Six patients required chemotherapy dose reduction; this occurred after the 9th cycle for 5 patients. Five patients required up to 7 days of treatment delay per cycle due to myelosuppression. Eight patients experienced NCI grade 1–3 abdominal pain within 48 hours of SIRT. Grade 3/4 neutropenia was seen in 10 patients. The nadir in mean leukopaenia levels was observed 2 months from SIRT. Grade 3 anaemia was observed in 1 patient. No significant thrombocytopenia was recorded. Peripheral neuropathy and gastrointestinal system adverse events were common, with grade 3/4 diarrhoea in 2 patients and grade 1/2 nausea in 12 patients. Grade 1 toxicity was observed in liver function tests measured in serum from 6 patients. Complete responses were measured by RECIST criteria in 2 of 17 patients, partial responses in 13 patients and stable disease in 2 patients, with no evidence of radiation hepatitis on contrast-enhanced computed tomography scans.
Conclusions: SIRT administration in combination with systemic FOLFOX4 is well tolerated by this patient group. The results suggest that studying the effect of chemoradiation with SIRT on response rate, local control and overall survival in patients with liver metastases from colorectal cancer is timely.

678 PUBLICATION

Local lymphocyte infiltration as a major prognostic factor in rectal cancer patients

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Background: In order to evaluate the relevance of various prognostic factors on the onset of relapse after radical resection of rectal cancer, the clinical history of 203 patients were analyzed.
Materials and methods: All the patients were affected with a low rectal cancer and all underwent a total rectal resection in combination with a complete mesorectal excision and a coloendoanal anastomosis.
Results: The pathological examination identified 43 Astler Coller B_1, 64 B_2, 21 C_1, and 75 C_2. patients. Despite the presence of lymphocyte infiltration

(TIL p: 0.0087) none of the other examined factors affected local recurrence rate in the present series: nodal status (NS p: 0.83), lateral spreading (LS.p: 0.76), lymphatic vessel invasion (LVI p: 0.347), blood vessel invasion (BVI p: 0.197), perineural invasion (PI p: 0.22). On the other hand overall survival is correlated with most of the above mentioned parameters and is inversely matched with the presence of lymphocyte infiltrate (TIL p:0.0001, NS p:0.0028, LS p:0.0067, LVI p: 0.058, BVI p: 0.352, PI p: 0.0003).
Conclusions: The present data are indicating the lymphocyte infiltration as a major prognostic factor in predicting the risk of local or distant relapse in rectal cancer patients.

679 PUBLICATION

Oncological results of hepatectomy associated with radiofrequency ablation of strictly unresectable liver metastases T in 63 patients with colorectal primary

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Background: Results and indications of intra-operative radiofrequency (RF) ablation of liver metastases (LM) are not well defined in the literature.
Aim: To appreciate the survival rate of patients with strictly unresectable LM (defined on technical but not oncological criteria) when undergoing liver resection plus RF, along with recent systemic chemotherapy.
Patients and methods: Sixty three patients with technically unresectable LM (either >5, or bilateral with no sparing at least one sector of the liver, or with tumor proximity to central major vascular structures) were treated by segmental anatomic resection (44 patients, 142 LM) when LM were large, with wedge resection (36 patients, 55 LM) when LM were peripheral and small, and with RF (63 patients, 154 LM) when LM were central and small. Extrahepatic metastases were also resected in 27%. All patients received perioperative chemotherapy. The median follow-up was 27.6 months (range: 15–74).
Results: There was no postoperative mortality and the morbidity rate was 27%. The 2-year overall survival rate of the 63 patients was 67% with a median survival of 36 months. In comparison, the median survival of similar patients treated classically with systemic chemotherapy alone is (was?)18 months. The local recurrence rates were similar for the 3 types of local treatments: 7.1% for the 154 RF ablations, 7.2% for the 55 wedge resections, and 9% for the 44 segmental anatomic resections (p = 0.216). Hepatic recurrences occurred in 71% of patients.
Conclusion: The combination of anatomic segmental resection, wedge resection, RF ablation, and recent systemic chemotherapy in patients with really unresectable LM results in a median survival of 36 months, and appears as a real improvement in survival.

680 PUBLICATION

Chemoradiation with raltitrexed in preoperative treatment of stage II/III resectable rectal cancer: long term results of a phase II study

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Background: Aim of this study is to evaluate the impact of a neodjuvant chemoradiation with raltitrexed on tumor response and long term results, in patients with locally advanced resectable rectal carcinoma.
Material and methods: Between 1998 and 2002, 39 patients were treated with preoperative chemoradiation, IV bolus of raltitrexed on days 1, 19 and 38 and concurrent 50.4 Gy (1.8 Gy/day) external beam radiotherapy. Surgery was performed 6–8 weeks after the end of chemoradiation. A 10 Gy IORT boost was delivered to the tumor bed. Patients with positive nodes at pathological examination underwent adjuvant with 5-FU-leucovorin (Machover regimen).
Results: All patients had T3 tumor at diagnosis, the N stage was: cN0 9 patients, cN1 19 patients and cN2 11 patients. All patients underwent surgery. The median follow-up was 58 months (range 34–79). Of 39 patients 24 (61%) downstaged at T level and 27 (69%) at N level. The pT stage was pT0 9 patients (23%), pTmic 7 patients (18%), pT1 2 patients (5%), pT2 6 patients (16%), pT3 13 patients (33%), and pT4 2 patients (5%). According to TRG (Tumor Regression Grade)classification patients were: TRG1 23% (9/39), TRG2 18% (7/39), TRG3 38% (15/39), and TRG4 21% (8/39). Five years OS was 91.7%, LC was 97.4% and MFS was 72.2%. Patients were grouped according pT (T0–2 vs T3–4), TRG (TRG1–2 vs TRG3–4), c N (cN1–2 vs cN2) and p N stage (pN0 and pN+). The cN stage wasn't statistically correlated with 5-year outcomes: OS was equal in the two group of patients; LC was 100% and 90.0% in cN0–1 and cN2, respectively; MFS was 78.5% in cN0–1 and 54.5% in cN2. Of postoperative parameters pT didn't show correlation with OS, a difference, even if not significant, was found for LC (100% in pT0–2 vs 93% in pT3–4) and MFS (82% in pT0–2 vs 58.7% in pT3–4); TRG showed a not statistical correlation with LC (100% in TRG1–2 vs 95.5% in TRG 3–4) and MFS (93.7% in TRG1–2 vs 61% in TRG 3–4), OS was equal in the 2 group of patients; pN was the strongest post-treatment factor in influencing the outcomes at 5 years: OS was 91.7% and 77% in pN0 and pN+ patients respectively (p = ns), LC was 97.4% and 90% in pN0 and pN+ patients respectively (p = ns), MFS was 72.2% and 52.6% in pN0 and pN+ patients respectively (p = 0.025).
Conclusion: Preoperative chemoradiation with raltitrexed showed and high rate of tumor downstaging, with an elevated percentage of pathological major response (pT0-mic 41%). Results were excellent in terms of OS and LC. The 5-years MFS was 72.2% and was statilstically correlated pN status. A longer follow-up is needed to confirm data. Validation of pretreatment prognostic factors will help to select patients to treat with more aggressive chemoradiotherapy combination.

681 PUBLICATION

Phase I study of concurrent chemoradiation including twice-weekly low dose gemcitabine for unresectable pancreatic adenocarcinoma

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Purpose: To determine the maximum tolerated dose (MTD) and dose-limiting toxicities, as well as potential antitumor activity of twice-weekly gemcitabine and concurrent irradiation in patients presenting with unresectable locally advanced, or metastatic and painful pancreatic adenocarcinoma.
Patients and methods: Thirty patients with histologically proven adenocarcinoma of the pancreas have been treated in Centre Hospitalier Lyon Sud, France, between 2000 and 2005. The initial dose of gemcitabine was 30 mg/m^2 by 30-minute intravenous infusion twice a week, for 5 consecutive weeks concurrent with 50 Gy of radiation within 5 weeks, delivered to the pancreatic area. Gemcitabine doses were escalated in 10 mg/m^2 increments in successive cohorts of three to six patients until dose-limiting toxicities were observed. A limiting toxicity is defined as a grade 4 or 5 toxicity.
Results: Thirty patients have been included, mean age 57 years old (41–73), 20 male and 10 female, 30 are evaluable for toxicity. Concurrent radiation and twice-weekly gemcitabine at 30-, 40-, 50-, 60-, 70 mg/m^2 were well tolerated, without limiting toxicities observed. All patients received the full dose of radiation, and 16/24 (67%) patients received at least 70% of the prescribed dose. This study currently explores the level 80 mg/m^2 twice a week.
Conclusions: This work is still in progress, until the MTD is reached. The complete cohort of patients will be finally analyzed for toxicity and for survival and relapse patterns, and will be followed by a phase II study to ascertain the feasibility of this scheme, with the recommended dose of twice-weekly gemcitabine, when evaluated. The next phase I trial will include oxaliplatin in addition to gemcitabine and radiation, for the same type of patients. Complete results will be presented during the meeting.

682 PUBLICATION

Laminin-5-gamma2-chain during the colorectal adenoma-carcinoma-sequence: from primary anchoring protein to an invasion promotor

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Background: The glycoprotein Laminin-5 is a key protein of the epithelial cell adhesion complex, providing cell anchoring to the basement membrane in normal colorectal mucosa. The γ2 chain of Laminin-5 (Ln-5 γ2) plays a pivotal role in cell migration and, possibly, as an invasion promotor in colorectal carcinomas. This study was performed to test whether there are and if yes, which changes occur in immunohistochemically detected Ln-5 γ2 pattern during the malignant transformation of colorectal adenomas.
Material and Methods: Paraffin specimens of full rectal wall specimens of low (n = 55) and high grade (n = 13) neoplastic colorectal adenomas, colorectal carcinomas (n = 37) and normal colon (n = 60) were assessed histopathologically and immunohistochemically for Ln-5 γ2 changes using the monoclonal antibody D4B5.
Results: A significant increase of immunohistochemically detected Ln-5 γ2-alterations associated with migration and invasion were described, i.e. loss of Ln-5 γ2 to the basement membrane, stromal deposition and intracellular increase of Ln-5 γ2 from low grade neoplastic adenoma to