dhiarrea, 2.9% astenia. The median follow-up time was 6.7 months. Disease-free survival and overall survival data are not avaliable yet.
Conclusions: Our preliminary results suggest that Capecitabine, Oxaliplatine and Irinotecan as first-line combination treatment in MCRC is a feasible and safe schedule with high antitumoral activity. More data will be presented when follow-up time increases.

708 PUBLICATION

Total pelvic exenteration for pelvic malignancies

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Introduction: Complete resection is the most important prognostic factor in surgery for pelvic tumours. In locally advanced and recurrent pelvic malignancies radical margins are sometimes difficult to obtain, because of close relation to or growth in adjacent organs/structures. Total pelvic exenteration (TPE) is an exenterative operation for these advanced tumours and involves en bloc resection of the rectum, bladder and internal genital organs (prostate/seminal vesicels or uterus).
Methods: Between 1990 and 2003 a TPE was performed in 47 patients with pelvic cancer; 29 rectal cancer (19 primary and 10 recurrent), 12 cervical cancer (2 primary and 10 recurrent), 4 sarcoma (2 primary and 2 recurrent), 1 primary vaginal – and 1 recurrent endometrial carcinoma. Eleven patients were previously treated with radiotherapy. Two patients were treated with neo-adjuvant chemotherapy. Thirty-three patients received pre-operative radiotherapy to induce downstaging of the tumour and three patients received post-operative radiotherapy. Thirteen patients received IORT because of an incomplete or marginal complete resection.
Results: The median follow up was 25 months (range 3–145). Median operation-duration, blood loss and hospitalisation were 440 min (range 300–670), 6300 ml (range 1100–21000) and 20 days (range 12–65). Overall major and minor complication rates were respectively 34% and 57%. The hospital mortality rate was 2%.
A complete resection was possible in 72% of all patients, a microscopically incomplete resection (R1) in 19% and a macroscopically incomplete resection (R2) in 9%.
Five-year local control for primary locally advanced rectal cancer, recurrent rectal cancer and recurrent cervical cancer was respectively 86%, 51% and 67%. Overall survival after 5 year for primary locally advanced rectal cancer, recurrent rectal cancer and recurrent cervical cancer was 46%, 23% and 67%.
Conclusion: Although total pelvic exenteration is accompanied with considerable morbidity, good local control and acceptable overall survival justifies the use of this extensive surgical technique in patients with primary locally advanced and recurrent pelvic tumours. New (neo)adjuvant treatment modalities will further improve complete resection rate, local and overall survival rate.

709 PUBLICATION

Preoperative radiotherapy and oral capecitabine improve surgical results in patients with locally advanced mid-lower rectal cancer

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Background: Preoperative chemoradiation increases the chances downstaging and downsizing of locally advanced rectal cancer and facilitates sphincter-saving procedures with significant impact on disease control and quality of life.
Material: 74 patients with T_{3-4} and/or N+ (according rectal endosonography) mid and low rectal adenocarcinomas were treated with preoperative chemoradiation consisted of capecitabine (825 mg/m^2) twice daily and radiotherapy in daily dose 1.8 Gy (25 days) followed by a boost up to 50.4 Gy. The patients were operated six weeks after finishing chemoradiation. Surgical procedures included total mesorectal excision and various modifications of stapled low colorectal anastomosis or abdominoperineal excision.
Results: Downstaging was observed in 73% of patients, 18% of patients had no residual disease. 19 abdominoperineal excisions and 53 low anterior resections were performed. Two anastomotic leaks were noticed during the postoperative period. One local recurrence has been registered so far. Two patients with complete remission are being observed without operation.
Conclusion: Preoperative chemoradiation with oral capecitabine works well in downsizing and downstaging of locally advanced rectal cancer and has resulted in more sphincter preservation operations and pelvic disease control with minimal perioperative and late morbidity. The impact on long-term disease control and survival requires further follow-up.

710 PUBLICATION

Cetuximab reversal of chemotherapy resistance in patients with extensively pretreated metastatic colorectal cancer treated at Paul-Brousse hospital

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Background: Cetuximab has demonstrated activity both as single agent and combined with irinotecan in patients (pts) with colorectal cancer (CRC) refractory to irinotecan (CPT-11) and oxaliplatin expressing epidermal growth factor receptor (EGFR). This retrospective study explored the activity and tolerability of cetuximab-5-fluorouracil-leucovorin (5-FU-LV) combined with CPT11 and /or oxaliplatin (l-OHP) in pts with CRC refractory to 5-FU-LV, CPT11 and l-OHP.
Methods: 37 pts were treated with cetuximab at 400 mg/m^2 loading dose over 2 hours, then 250 mg/m^2 over 1 hour weekly. Cetuximab was given alone (1 pt) or combined with CPT11–5-FU-LV +/-l-OHP (29 pts) or l-OHP-5-FU-LV (7 pts) given as conventional (5 pts) or chronomodulated infusions (31 pts). EGFR status (0 vs 1–10 vs >10% positive cells) was determined with Dako (12 pts), Zymed (17 pts) or Ventana (8 pts). Toxicity was graded every 2–3 weeks (Common Toxicity Criteria). Response was assessed with CT scan every 2 months (RECIST criteria).
Results: 28 pts with EGFR+ and 9 pts with EGFR− CRC received treatment as 3rd line or beyond. Median age 64 y; M/F: 16/21; WHO performance status 0/1/2: 20/14/3; colon/rectum: 23/14; ⩾2 metastatic sites: 30 pts. Cetuximab was withdrawn for allergic reaction during 1st course in 5 pts. Any grade 3–4 toxicities were encountered in 47.5% of the pts. The major toxic effect was acneiform skin rash which occurred in 20 pts (grade 2: 12 pts, 32.4%; grade 3, 8 pts, 21.6%). Four pts are not assessable for response (no measurable disease: 1 pt; too early: 3 pts). Of 33 pts, treatment failed in 10 pts (30.3%), disease was stable in 12 pts (36.4%), partial responses (RECIST criteria) occurred in 9 pts (27.3%) and complete responses in 2 pts (6%). Response rate was 33.3% [95% CL: 17 to 49.7%]. Disease was controlled (response or stabilization) in 23 pts (69.7%). No obvious relation was found between: 1) EGFR status and response (EGFR 0%, 1 CR / 5 pts; EGFR 1–10%, 6 PR /14 pts; EGFR >10%, 1 CR & 3 PR /9 pts) or 2) grade of acneiform rash and response (grade 0–1, 5/11 pts; grade 2, 3/11 pts; grade 3, 3/6 pts).
Conclusions: The combination of cetuximab with the chemotherapy regimens here administered apparently increased response rate with acceptable tolerability as compared to that reported in the BOND study. This supports a supradditive effect of cetuximab which here appeared as unrelated with immunohistochemistry-assessed EGFR status or grade of acneiform reaction.

Oral presentations (Thu, 3 Nov, 8.30–10.30)
GI – GIST tumours

711 ORAL

Imatinib mesylate in advanced Gastrointestinal Stromal Tumors (GIST): survival analysis of the intergroup EORTC/ISG/AGITG randomized trial in 946 patients

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Background: From 2/2001 to 2/2002, 946 patients (pts) with a diagnosis of advanced GIST were randomized to Imatinib at two dose levels within a

trial by the EORTC Soft Tissue and Bone Sarcoma Group (STBSG), the Italian Sarcoma Group (ISG), and the Australasian Gastro-Intestinal Trials Group (AGITG). Progression-free survival (PFS) data at a median follow-up of 25 months have been published (Verweij J et al, Lancet 2004; 364: 1127). At a median follow-up of 40 months, the number of events has now allowed an overall survival (OS) analysis.
Patients and Methods: 946 pts with locally advanced and/or metastatic GIST were randomly allocated to Imatinib mesylate 400 mg or 800 mg daily. Pts progressing at 400 mg were eligible for cross-over to 800 mg. Age was 18–91 yrs, PS 0–3, M/F ratio was 61% / 39%. Mutational analysis data were available for a subset of 377 pts with suitable material.
Results: At a median follow-up of 40 months, median OS was still not reached, and OS at 3 years was = 59%. Median PFS was 22 months, and PFS at 3 years was = 33%. There was no significant difference in OS between the two arms. At a longer follow-up, the previously reported PFS advantage for the high-dose arm was not statistically significant for long-term PFS. In the subset of pts with mutational analysis, c-kit exon 9 mutation or wild type predicted a significantly worse OS, as compared to exon 11 mutations. Largest tumor diameter and granulocyte count were the most consistent predictors for OS across prognostic models, along with age, PS, initial hemoglobin and albumin level, and prior chemotherapy. None of these factors was associated to significant differences in OS in favour of the high dose arm, save for disease origin outside stomach / small bowel. A trend towards better OS for the high dose arm amongst exon 9 mutants was not statistically significant at this median follow-up, though against a strong advantage in terms of early PFS (Debiec Rychter M et al, in press).
Conclusions: Imatinib mesylate provides an obvious OS advantage to advanced GIST pts, with a median OS still not reached at 3 years, though against a PFS in the 30% range. OS was not affected by the dose level at treatment start, though the cross-over study design allowed some progressing pts to benefit from dose escalation (Zalcberg J et al, in press). Prognostic factors for OS seem to be associated to 1) mutational status, and 2) initial disease extent. The group of pts with exon 9 mutation needs to be dealt with separately.

712 ORAL

Clinical outcome in gastrointestinal stromal tumor patients who interrupted imatinib after achieving stable disease or better response

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Background: Imatinib has become standard therapy for patients with gastrointestinal stromal tumor (GIST) and it is usually given until progressive disease (PD) or patient intolerance. It is not known if patients with GIST controlled with imatinib will require continuous therapy, or whether imatinib could be safely discontinued in these situations. The aim of the current study is to evaluate the clinical outcome of imatinib interruption in GIST patients who achieved stable disease or better response to imatinib therapy.
Methods: From July 2001 to December 2004, we prospectively gathered clinical data from 62 consecutive patients with metastatic or unresectable GIST. Fifty-eight (93.5%) achieved stable disease or better response to imatinib therapy and 14 of them interrupted imatinib therapy because of patients will or physician's discretion and are included in this study. Median time to imatinib interruption after the onset of imatinib therapy was 11.9 months. Progression free survival (PFS) after imatinib interruption was calculated and imatinib-refractory PFS was compared between the interrupted imatinib group and continuous imatinib group.
Results: With a median FU duration of 17.9 months after imatinib interruption, nine patients (64%) had PD. Median PFS was 10.0 months (95% CI, 5.6–14.5 months). There was significant difference in PFS between the groups (P = 0.029). Median PFS was not reached in the continuous group and 21.8 months (95% CI, 17.3–26.3 months) for the interruption group. Eighty-eight percent of patients had the second disease control with the imatinib reintroduction.. There were no significant differences in imatinib-refractory PFS and overall survival (OS) between the groups (P = 0.405, P = 0.498).
Conclusion: In the patients with advanced GIST controlled with imatinib, imatinib interruption resulted in the high risk of PD within one year. However, the majority of the disease was controlled with imatinib re-challenge on PD and there were no significant differences in imatinib-refractory PFS and OS between groups. Imatinib may be interrupted, at least temporarily, in patients with GIST controlled with it when various clinical situations constrain continuous treatment.

713 ORAL

Interruption of Imatinib (IM) in responding patients after one year treatment does not influence overall survival of patients with advanced GIST: Updated results of the French Sarcoma Group randomized phase III BFR14 trial

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Background: IM (Gleevec/Glivec®; Novartis Pharma) the front-line treatment (Tx) for advanced GIST seems to be given continuously until disease progression (PD) or intolerance. IM interruption in responding patients (pts) was significantly associated with a poor PFS. The impact of IM re-introduction was evaluated both on response and overall survival.
Methods: This prospective multicenter BFR14 study was initiated in June 2002. After 1 year of IM 400 mg/day, 58 pts free from progression were randomly offered to continue or interrupt Tx until PD. Pts allocated to the interruption (I) arm could restart IM (same dose) in case of PD. Primary endpoint was progression-free survival (PFS); secondary endpoints were OS, quality of life (QoL), secondary response after IM re-introduction, identification of molecular determinants of response. Survival data were compared using the log-rank test.
Results: Patient characteristics were well balanced between the two arms. Current median follow-up after inclusion and randomization are 21 and 12 months respectively. 24/32 pts (75%) in arm I versus 6/26 pts (23%) in continuous (C) arm experienced PD. (P < 10−4) with a median of 6 months (95% CI, 3–9) for arm I. IM reintroduction (median: 5.7 months after randomization) allowed tumor control (OR or SD) in 19/22 evaluated pts (86%). One-year OS rates were 93% and 95% for arms I and C, respectively (P = 0.6), with no significant difference in QoL.
Conclusions: IM reintroduction in GIST patients was safe and allowed a similar tumor control rate than in front-line treatment (86%). The one year OS rates were 93% and 95% for the experimental and control arms, respectively (p = 0.6) A transient interruption of IM in elderly patients will advanced GIST and/or in patients exhibiting a grade 3–4 toxicity could be a therapeutic option. GIST mutational analysis of the 58 randomized patients is ongoing. A new randomization (same schedule) is planned after 3 years of IM in non progressive patients

714 ORAL

FDG-PET imaging demonstrates kinase target inhibition by sunitinib malate (SU11248) in GIST patients resistant to or intolerant of imatinib mesylate

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Background: The purpose of this study was to use FDG-PET to image tumor metabolism before and after treatment with sunitinib malate in GIST patients after failure of imatinib mesylate (IM) therapy due to resistance or intolerance, as an early indicator of clinical activity.
Materials and methods: Sunitinib is an oral multitargeted tyrosine kinase inhibitor of VEGFR, PDGFR, KIT, RET and FLT3 with antiangiogenic and antitumor activities. 97 IM-resistant or intolerant GIST patients received 1 of 3 schedules of daily sunitinib: 25–75 mg, 2 weeks on/2 weeks off; 50 mg, 4 weeks on/2 weeks off; or 50 mg, 2 weeks on/1 week off. FDG-PET was performed on 75 of these patients at baseline (scan 0, n = 74), after 7 days on therapy (scan 1, n = 61), after the first period off therapy (scan 2, n = 51) and after subsequent cycles while on treatment (scan 3, n = 8 and scan 4, n = 28). Maximum standardized uptake value (SUVmax) was measured in the lesions with the greatest uptake (⩽5 lesions per patient) in these 75 patients. SUVmax measurements were transformed by log base 10 to improve model fit, and a linear mixed effects model was used to estimate log SUVmax at each time point. This model accounts for correlated lesions and repeated measures over time. Linear contrasts were used for pair-wise comparisons.
Results: Model-based estimates of mean log SUVmax values (±SE, n = 75 patients) for the 5 time points were: 0.91 (±0.03), 0.63 (±0.03), 0.78 (±0.03), 0.64 (±0.06) and 0.57 (±0.03). Comparisons of mean log SUVmax at different scan times are shown in the table. Mean log SUVmax was significantly lower after periods of sunitinib treatment than at baseline or at the end of the period off treatment.