exclusion of fit elderly patients from clinical studies and also to the total lack of studies in unfit elderly, who represent at least 50% of the geriatric population presenting into major hospitals.

Methods: We analysed a database of 3825 patients treated within different European trials for the prognosis of elderly (> 70 years, n= 711) and non-elderly patients (<= 70 years, n=3114).

Results: There was a difference in the percentage of elderly patients included in the different European countries: the highest rate in Austria (38%) and lowest in the UK (3%), Germany had 13% and overall 19% of patients were above 70 years of age. The distrubution of age groups was as follows: 70-75 years 370 pts, 75-80 years 116 pts, > 80 years 20 pts (only 1 patient above 85 years). Elderly patients had a higher incidence of rectal primary (p=0.01), more frequent weight loss (p=0.03) and more prior adjuvant chemotherapy (p<0.0001). Significant prognostic factors (Köhne et al. ASCO 2000) like WBC, thrombocytosis, alkaline phosphastase and LDH all were in favour of elderly patients, however the distribution into good (52% vs. 73%), intermediate (27% vs. 26%) or poor risk (21% vs. 21%) of non-elderly and elderly patients did not differ significantly. Objective responses were more likely to occur in elderly patients (26% vs. 21%, p=0.005). Relapse free survival (5.3 vs. 5.8 months, p<0.0001) and overall survival (11.1 vs. 12.0 months, p<0.001) were all in favour of elderly patients with insignificant clinical albeit statistical significance. Survival of elderly vs. non-elderly patients in the three previously defined risk groups did not differ. Older age was also not an independent prognostic parameter.

Conclusions: Fit elderly patients should not be excluded from clinical trials and studies in unfit elderly patients are warranted and currently discussed by The International Society of Geriatric Oncology (SIOG) and DGHO elderly group. Elderly patients need more attention regarding their functional, social and mental status.

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Capecitabine plus oxaliplatin (XELOX): findings from a human colon cancer xenograft model and a phase II clinical trial in patients with metastatic colorectal cancer (MCRC)

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Background: Capecitabine (Xeloda®, an oral tumoractivated fluoropyrimidine, is replacing i.v. 5-FU as first-line therapy in MCRC based on its high single-agent activity (response rate [RR] 26%) and improved safety compared with bolus 5-FU/LV. With other advantages in terms of convenience and patient preference for oral therapy, capecitabine could also replace i.v. 5-FU in combination regimens. Adding oxaliplatin (single agent RR approx. 10%) to infused 5-FU/LV improves efficacy in patients with MCRC. Since capecitabine and oxaliplatin have key toxicities that do not overlap, capecitabine is an attractive combination partner for oxaliplatin.

Preclinical Study: The antitumor activity of XELOX was evaluated in mice with CXF280 human colon cancer xenograft. Capecitabine was administered p.o. on days 1-14 plus oxaliplatin i.v. on day 1, every 21 days. Combining capecitabine and oxaliplatin produced at least additive antitumor activity. XELOX at two-thirds of the maximum tolerated dose (MTD) for each agent was more potent than either single agent at their MTD. Furthermore, oxaliplatin upregulated the tumor level of thymidine phosphorylase (TP), the final enzyme in the conversion of capecitabine to 5-FU. This upregulation of TP by oxaliplatin was not observed in two further colon cancer xenograft models that were unresponsive to oxaliplatin.

Phase II Clinical Study: 96 patients (61 men, 35 women) received i.v. oxaliplatin (130 mg/m^2, day 1) plus oral capecitabine (1000 mg/m^2, twice daily on days 1-14) every 21 days as first-line treatment for MCRC. Median age was 64; colon cancer (63%)/rectal cancer (33%)/both (4%); 54% had >1 metastatic site; 77%, 39% and 32% had liver, lymph node or lung metastases, respectively; 28% had received adjuvant fluoropyrimidines. All patients were evaluable for efficacy and safety. RR was 55% (95% CI, 45-65%) and 31% of patients had SD >3 months. Median TTP was 7.6 months (95% CI, 6.4-8.6 months) and median overall survival was 19.5 months. Grade 3/4 toxicities were sensory neuropathy (16%), diarrhea (16%), nausea/vomiting (13%), asthenia (9%), neuropathic pain (6%), neutropenia (7%), and thrombocytopenia (4%). Grade 3 hand-foot syndrome affected only 3% of patients and 60-day all cause mortality was 2.1%.

Conclusions: The clinical findings (RR 55% and good tolerability) confirm the preclinical observations in human colon cancer xenografts and indicate that XELOX is a highly active and appropriate first-line treatment for MCRC.

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Capecitabine plus irinotecan (XELIRI) in first line metastatic colorectal cancer (MCRC): update on a phase II trial

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Background: Capecitabine (Xeloda®), a tumor-activated oral fluoropyrimidine, has superior activity and an improved safety profile compared to 5-FU/LV in 1st line MCRC. Adding irinotecan (CPT) to bolus or infused 5-FU/LV improves efficacy, but safety appears better with infused 5-FU. However, infused combinations are burdensome and time-consuming for patients and healthcare providers alike. Mimicking infusion with twice-daily oral administration, capecitabine can replace infused 5-FU in combination therapy. The combination of capecitabine (X) and CPT should be an effective, safe, and more convenient 1st line option.

Materials and methods: Recommended doses were identified in 2 independent phase I trials [1]: intravenous CPT (250 mg/m^2 d1) followed by intermittent oral X (1000 mg/m^2 twice-daily for 14 days) every 3 weeks, from evening day 1 to morning day 15. To improve safety and permit treatment of older patients (pts), those ≥ 65 years old received lower doses of both agents (200/750). Objectives were to evaluate efficacy and safety in 1st line MCRC pts.

Results: Accrual is complete (n=52). 51 patients are evaluable for safety and 43 for response: 29 men (56%), 23 women (44%); median Karnofsky PS 90 (70-100), median age 57.5 (30-79). 44 pts (85%) had colon cancer, 6 rectal (11%) and 2 both (4%). Tumor differentiation was 15% poor, 64% moderate, 11% well and 10% unknown. 41 pts (79%) had liver metastases and 31 (60%) had stage IV disease at initial diagnosis. 10 pts (19%) received prior adjuvant 5-FU. Median number of treatment cycles is currently 5 (70% ≥ 4 cycles, 44% ≥ 6, 14% = maximum of 12 cycles) with a median follow-up of 39 weeks (range, 11 to 68 weeks). Most common (>5%) AEs (all grade 3) were diarrhea 22%, nausea/vomiting 12%, dehydration 12% (1 pt with grade 4), hand-foot syndrome 6%. Grade 3 or 4 neutropenia was seen in 18%. There were no treatment-related deaths. Response rate was 18/43 (42%) with another 17 stabilizations (39%, including 8 unconfirmed responses, giving tumor control in 8/10 patients). In one center, 8 patients were able to undergo potentially-curative resection following their chemotherapy. Median time to progression (TTP) is currently 6.4 months (range, 1-13).

Conclusion: X should replace 5-FU in combination with CPT to create an effective, safe, and less burdensome treatment option in 1st line MCRC. XELIRI compares favorably with standard CPT/5-FU/LV combination regimens in terms of response rate and TTP. Updated results will be presented.

Reference

[1] Kerr et al, Delord et al. ASCO 02 abstracts 643 & 397

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Twelve weeks of neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation (CRT) and total mesorectal excision (TME) in MRI defined poor risk locally advanced rectal cancer resulted in promising tumour regression and rapid symptomatic relief

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Purpose: To evaluate neoadjuvant capecitabine/oxaliplatin prior to CRT and TME in newly diagnosed patients with MRI defined poor risk/locally advanced rectal cancer. Patients and Methods: MRI criteria for poor risk rectal cancer were: tumours within 2mm of mesorectal fascia i.e. circumferential resection margin (CRM) threatened; T3 tumours at/below levators; tumours extending more than or equal to 5mm into peri-rectal fat;

T4 tumours and T1-4N2 tumours. Patients received 12 weeks of neoadjuvant capecitabine (2000mg/m2/day po for 14 days every 3 weeks) and oxaliplatin (130mg/m2 iv every 3 weeks). Starting on week 13, capecitabine was continued at 1650mg/m2/day continuously with concomitant radiotherapy 45Gy in 25 fractions followed by 5.4-9 Gy boost to primary tumour. TME was planned 6 weeks after chemoradiation. Post-operatively, patients received 12 weeks of capecitabine at 2500mg/m2/day for 14 days every 3 weeks. MRI was repeated after chemotherapy and CRT.

Results: Between November 01 and November 02, 22 patients were recruited. Median age was 62 (range=38-80). 21 patients had tumour threatening CRM. 19 patients were evaluable for radiological response and 18 patients have proceeded to TME. Following neoadjuvant capecitabine/oxaliplatin, all patients had objective responses (1 CR, 18 PRs). In addition, 80% of patients had symptomatic responses in a median of 22 days (i.e. after one cycle of chemotherapy) including reduced rectal bleeding (100%), improvement in diarrhoea/constipation (79%), diminished pelvic pain/tenesmus (64%) and weight gain/stabilisation (100%). Following CRT, tumour response was sustained in all patients. One patient was still inoperable, but all other patients had R0 resection with tumour regression away from the CRM. Pathological CR was found in 5 patients (28%) and in an additional 8 patients (44%), only microscopic tumour foci were found on surgical specimens. One patient died from myocardial infarction and 1 from pulmonary embolism. No grade 4 toxicity occurred during chemotherapy or CRT.

Conclusion: Capecitabine and oxaliplatin prior to synchronous CRT and TME produces almost universal tumour regression, rapid symptomatic response and may facilitate the achievement of R0 resection.

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Optimox study: Folfox7 compared to Folfox4 in metastatic colorectal cancer (CRC). Results of a randomized study.

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Background: FOLFOX4 has shown superiority over LV5FU2 in first-line therapy of metastatic CRC (de Gramont; J Clin Oncol 18:2938-2947, 2000). The limiting toxicity of the FOLFOX4 regimen is a cumulative sensory neurotoxicity which imposes to stop therapy in patients still responding. In the OPTIMOX study, a limited number of cycles (6 cycles of FOLFOX7) was administered to decrease the neurotoxicity and to later allow FOLFOX reintroduction.

Materials and methods: Patients (pts) were randomised between (arm A) FOLFOX4: oxaliplatin 85 mg/m^2 day (d)1, and folinic acid, 200 mg/m^2 d1 and d2, 5FU bolus 400 mg/m^2, followed by 5FU 22h continuous infusion 600 mg/m^2 d1 and d2 every two weeks and (arm B) FOLFOX7: oxaliplatin 130 mg/m^2 day (d)1, and folinic acid, 400 mg/m^2 d1 only, followed by 5FU 46h continuous infusion 2400 mg/m^2 every two weeks for 6 cycles followed by sLV5FU2: folinic acid, 400 mg/m^2 d1, 5FU bolus 400 mg/m^2, followed by 5FU 46h continuous infusion 2400-3000 mg/m^2 every two weeks for 12 cycles. FOLFOX7 was then reintroduced for 6 cycles or earlier in case of progression on sLV5FU2 in patients having a response or stable disease at the first FOLFOX administration. 623 pts have been enrolled. Arm A, 312 pts (%): M/F=59/41, PS 0/1/2=52/39/8, median age=63[29-80]; Arm B, 313 pts (%): M/F=61/39, PS 0/1/2=53/38/9, median age=64[32-80].

Results: Grade 3-4 toxicity (% of pts) was in arm A (FOLFOX4)/arm B (FOLFOX7): neutrophils 26/20, platelets 3/11, nausea 4/7, mucositis 2/4, diarrhea 9/9, hand-foot 0/2, alopecia 0/4, neurotoxicity 13/13, fatigue 1/1. Response rate (409 evaluated pts) was 58% in arm A (FOLFOX4) and 64% in arm B (FOLFOX7). Progression at first evaluation was 9% in arm A and 7% in arm B. The primary endpoint is the time to disease control (TDC) which is the progression-free survival of FOLFOX4 or FOLFOX7-sLV5FU2 plus the progression-free survival (PFS) of FOLFOX reintroduction in case of second response or stabilization. Median TDC was 10.3 months in arm A and 12.3 in arm B.

Conclusions: FOLFOX7 followed by sLV5FU2 has similar toxicity and efficacy than FOLFOX4 and is a more convenient regimen. Updated data for the whole population should be available for the meeting concerning Response Rate, PFS, TDC, % of surgery of metastasis and FOLFOX7 reintroduction.

Central nervous system tumours

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Upregulation of HC gp-39 gene in astrocytic gliomas

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Background: Astrocytic gliomas are highly malignant, lethal and the most common glial tumors of the central nervous system. Present knowledge recognizes only a fraction of the biological mechanisms presumably to initiate and promote astrocytic glioma formation. Changes in gene expression are important determinants of normal cellular physiology and, if disturbed, directly contribute to abnormal cellular physiology, including cancer. In this context, the identification, cloning and characterization of differentially expressed genes can be expected to provide relevant and important insights into the molecular determinants of tumor initiation and progression.

Materials and Methods: Serial Analysis of Gene Expression (SAGE) has been used for the comparison of gene expression profiles between normal brain and glioblastoma multiforme (GBM). Expression levels of about 47000 genes represented by approximately 284000 of 10 bp "tags" in normal brain and GBM SAGE libraries were compared by accessing SAGEmap database of NCBI. Northern blot hybridization was used for verification of SAGE results.

Results: SAGE showed that human cartilage glycoprotein-39 gene (HC gp-39) had the greatest change in tumour cells. The abundance of HC gp-39 tags was 82 fold higher in GBM library. Northern analysis of brain tumour and normal brain tissue panels confirmed the results of SAGE and showed very high expression levels of HC gp-39 gene found exclusively in astrocytomas of higher grades, anaplastic astrocytoma and GBM. Overexpression of this gene was detected in 14 of 16 GBMs and 6 of 16 anaplastic astrocytomas analyzed. Two GBM samples revealed lower content of HC gp-39 mRNA as compared to other 14 GBM samples but still higher than in normal brain. Low level of HC gp-39 mRNA was detected in samples of normal brain adjacent to anaplastic astrocytomas and GBMs, this mRNA was not detectable at all in WHO grade II astrocytomas and in adjacent normal brain samples. It was not also detected in other brain tumour types. In addition to 1.7 kb mRNA present in all positive cases and found in human chondrocytes and synoviocytes, Northern blot hybridization revealed the larger-sized transcript of HC gp-39. This larger-sized transcript was associated mostly with astrocytomas of higher grades and could arise from alternative processing that may alter the translation product or regulate mRNA stability.

Conclusion: The overexpression of HC gp-39 gene and the appearance of larger-sized transcript may be an important feature of higher grades astrocytomas and can be used as an additional factor for distinguishing between astrocytomas and anaplastic astrocytoma or between GBM and other types of human brain tumours in the cases of ambiguous histological diagnosis.

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Inverse planned stereotactic intensity modulated radiation therapy (IMRT) in the treatment of complex shaped benign meningiomas of the skull base: Acute-, late toxicity and preliminary results.

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Purpose/Objective: The efficiency of radiotherapy for the primary treatment of benign meningiomas and as adjuvant treatment for subtotally resected or recurrent meningiomas has been demonstrated by large modern series. But by using conventional radiotherapy and even stereotactic radiotherapy it is difficult to achieve doses of more than 54 Gy which allows excellent long time control rates, without exceeding the tolerance doses of the surrounding critical normal structures. The aim of this clinical phase I study is to establish inverse treatment planning and IMRT for complex shaped meningiomas of the skull base in the daily clinical routine. Further objectives of this study were to assess the safety, the efficiency and the side effects of inverse planned stereotactic IMRT in the treatment of benign meningiomas of the base of skull.