1143 PUBLICATION

Phase I and pharmacokinetic (PK) study of irinotecan (CPT11) with a prolonged (14D) infusion schedule

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CPT11 isa a topoisomerase I inhibitor with substantial anti tumor activity. Preclinical data suggest that prolonged exposure has better efficacy and possibly less toxicity. A dose-escalation phase I study of CPT11 continuous i.v (c.i.v.) over 14-days every 3 to 5 weeks was conducted in order to determine the maximal tolerated dose (MTD). Since March 1996, 15 patients (pt) have been enrolled with the following characteristics: median age: 57 (range 29–70); median PS 1 (range 0–2); sex: 12 F/3 M, primary sites: colorectal cancer 8, unknown primary 1, other 6; all heavily pre-treated. Only 10 patients evaluable for toxicity and PK. Already at the first dose of 12.5 mg/m^2/d dose limiting toxicity was encountered consisting of cumulative gr 3–4 diarrhea 3/5 pt and gr 3–4 neutropenia 2/5 pt. At a dose of 10 mg/m^2/d 1/4 pt had gr 4 diarrhea (despite high dose of loperamide) and myelosuppression was not dose limiting. Other side effects were moderate: fatigue 2 pt, thrombocytopenia 1 pt; alopecia was minimal. One response (not yet confirmed) in colorectal cancer was observed. Substantial interpatient and intrapatient variability in systemic exposure was observed. The mean total AUC of CPT11 was 8.9 ± 5.4 and 8.0 ±0.2 h.μg/ml at 12.5 and 10 mg/m^2/d respectively. For SN38 AUC values were 0.93 ± 0.47 and 0.59 ± 0.06 h.μg/ml. The active lactone forms of CPT11 and SN38 accounted for by 36 ± 9% and 64 ± 6% respectively, of total drug exposure. At 12.5 mg/m^2/d, plasma levels were higher during the second course. This increase was not due to changes in the fraction of CPT11 metabolized to SN38 which was stable over both courses (mean values: 10.3 ± 5.1 and 8.0 ± 1.7% at 12.5 and 10 mg/m^2/d respectively). The MTD of this schedule (175 mg/m^2) is much lower than that with short infusion (350 mg/m^2). AUC metabolic ratio SN38/CPT11 is higher and a cumulative effect was observed. The dose of 140 mg/m^2/d leads to a SN38 AUC close to that of 350 mg/m^2 short infusion (0.59 vs 0.45 μg/ml) and is probably the recommended dose.

The dose of 10 mg/m^2 over a 17–21-days c.i.v. is under evaluation.

1144 PUBLICATION

Effect of food on the pharmacokinetics of toremifene

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Purpose: This study was designed to determine the effect of food on the bioavailability of toremifene citrate administered orally as a 60 mg tablet to healthy volunteers.

Methods: In a two-way crossover trial, 12 young healthy male subjects received a single 60 mg dose of toremifene, once after a 14-hour fast, and once following a standard high-fat meal. Serum samples were obtained periodically, 0–28 days post-dose. Serum levels of toremifene and its metabolites were determined using an HPLC method.

Results: Under fasted conditions C_{max}, t_{max}, AUC and $t_{1/2}$ for toremifene were 194 ng/mL, 2.3 h, 9482 ng h/mL and 99 h, respectively. Under fed conditions t_{max} was delayed to 4.0 h, but C_{max}, AUC and $t_{1/2}$ values were not significantly different. Likewise, pharmacokinetic parameters for the active toremifene metabolite, N-demethyltoremifene, were similar under fed and fasted conditions

Conclusion: Since the extent of toremifene absorption remains constant, and the drug has a relatively long half-life, the drug can be taken equally well in fasted conditions or with meals.

1145 PUBLICATION

Low toxicity (TOX) of a prolonged infusion of gemcitabine (GEM)

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Purpose: Pharmacologic studies suggest that due to a saturable formation of the active metabolite prolonged infusion time rather than an increased dose of gem, a novel nucleoside analog, should lead to increased exposure to the active drug. This strategy appears to be promising provided that the tox is as favorable as with short time infusion of this drug.

Methods: In phase I studies we examined the tox profile of single agent gem (200 mg/m2) administered as a 360-minute infusion once a week for 3 consecutive weeks followed by a week of rest (one cycle). Five heavily pretreated men (aged 25–66 ys) with advanced soft tissue sarkomas und 3 chemonaive women (aged 56–61 ys) with metastatic breast cancer received a total of 22 cycles (median 3; range 1–6) of this treatment.

Results: Except for 1 WHO grade 3 nausea and 1 grade 3 edema no further grade 3 or 4 non-hematological tox occurred. Further low grade tox were liver (n = 6), flu-like symptoms (n = 1), alopecia, nausea and proteinuria. As expected hematological tox was higher in pretreated compared with chemonaive pts with 2 grade 3 anemias and 1 leucopenia. Other hematological tox which consisted mainly of thrombocytopenia and granulocytopenia was mild and short-lived. Only 2 administrations of gem had to be postponed due to tox.

Conclusion: Even in heavily pretreated pts prolonged infusion of 200 mg/m2 gem for 360 min is well tolerated and administration appears not to be limited by a cumulative tox. Dose escalation studies with this schedule are under way.

Head and neck cancer II

1146 ORAL

Clinical radiobiology of glottic T_1 squamous cell carcinoma

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Background: T_1 glottic cancers form a homogenous group of tumours. This homogeneity enables the quantitative estimation of radiobiological parameters.

Methods: Retrospective analysis of 235 cases of laryngeal T_1 glottic squamous cell carcinoma treated with radiation alone was performed using the maximum likelihood estimations, and the Poisson-LQ/log-logistic mixed models.

Results: Mixed model gave the median latent time of recurrence of 16 months, the initial D_0 ($1/\alpha$) 4.5 Gy, the repopulated fraction (λ/α) 0.35 Gy/day, and the initial number of functional clonogens of 9000. The best estimate of α/β value is equal to 18 Gy and the TCD_{50} is equal to 57 Gy. For the conventional treatment (66 Gy, 2 Gy per fraction) both the estimated TCP and the observed control rate is equal to 90% when the overall treatment is not prolonged. Ten day prolongation of the treatment time results in about 11% decrease of TCP. Although the repopulated fraction is lower than previously estimated (0.6 Gy/day for supraglottis), the dose response curve is steep and the decrease of TCP is substantial when the treatment time is prolonged. A significant correlation between the haemoglobin concentration and TCP was found.

Conclusions: Both the treatment time and the haemoglobin concentration influence the outcome of RT because of glottic T_1 carcinoma.

1147 ORAL

Cost-effectiveness in T1N0 glottic squamous cell carcinomas (SCC): Comparison between radiotherapy (RT), laser microsurgery (L) and partial laryngectomy (PL)

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Purpose: A cost minimisation analysis of three non-mutilating treatments, RT, L or PL, which have been shown to be equally effective options for T1N0 glottic SCC was carried out..

Methods: For each treatment, the various events associated with the diagnostic procedure, the primary treatment, the complications, and the salvage treatment were individualized. The cost of each of these events weighted for the frequency of application based on the standard management procedure used in our institution and review of the published data, was then determined using the "fee for service" policy established by the National Health Insurance of Belgium.

Results: A total cost of 226, 250 and 457 kBEF were calculated for RT, L and PL, respectively. For L, cost included the cost of post-operative RT applied in case of positive margins (30%). For PL, the cost of the primary treatment accounted for 70% of the total cost whereas it only accounted for 47% and 39% for L and RT, respectively. For RT, L or PL, complications accounted for less than 10% of the total cost. The cost of salvage treatment reached 26%, 18% and 6% of the total cost for RT, L and PL, respectively.