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.

Conclusions: RT and L have almost the same expected average cost for the treatment of T1N0 glottic SCC, whereas PL is twice as expensive. Cost-effectiveness analysis (with voice quality as effectiveness parameter) is in progress.

1148 ORAL

Larynx conservation in a randomized trial of hyperfractionated (HFRT) versus conventional once daily radiation (CRT): A subgroup analysis

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Purpose: To examine the ability of HFRT and CRT to conserve the larynx in patients with advanced laryngeal cancer.

Methods: Between 1988 and 1995, 336 patients with locally advanced cancers of the larynx, hypopharynx or oropharynx were randomized to receive radiation therapy (RT) with curative intent. A subset of 116 patients had category T3 or T4 (UICC-AJC 1987) primary larynx cancer. Treatment was either 51Gy TAD/20 fractions/4 wk (2.55 Gy 1×/d = CRT) or 58 Gy TAD/40 fractions/4 wk (1.45 Gy 2×/d, 6 hr interval, = HFRT). Surgical salvage was performed for residual cancer whenever possible.

Results: The primary cancer arose in the glottis in 30, and in the supraglottis in 86; 51 tumors were T3 and 65 were T4. The local recurrence free rates at 3 yr were 50% (CRT) and 54% (HFRT) (Log rank p = 0.46). Local control was achieved in 46% (24/52) of those who had tracheostomy prior to RT. The overall survival rates at 3 yr were 47% (CRT) and 69% (HFRT) (p = 0.04). No patient experienced toxicity which required laryngectomy.

Conclusion: In this subset analysis there is no significant advantage of HFRT over CRT at the doses given with respect to control of advanced laryngeal cancer. Both fractionation schemes proved capable of preserving the larynx in more than 50% of patients with either T3 or T4 cancer. Prior tracheostomy did not prevent larynx conservation by RT.

1149 ORAL

Organ preservation and survival with surgical treatment for larynx carcinoma

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Objective: This prospective study evaluates the potential role of organ sparing surgical procedures for larynx carcinoma in a large series of unselected patients from a single institution.

Patients and Methods: 504 consecutive patients with previously untreated carcinoma of the larynx were seen from 1986 to 1994. The treatment protocol included transoral laser surgery (TLS) of the primary for lesions classified T1/T2; conventional partial laryngectomies for these lesions if they were not accessible endoscopically; total laryngectomy for most lesions classified T3/T4; and radiotherapy for patients not suited for surgery.

Results: TLS was used in 290 patients (58%), total laryngectomy in 130 (26%), conventional partial laryngecomies in 31 (6%), radiotherapy in 34 (7%). Nineteen (4%) had no curative treatment. Five-year uncorrected actuarial survival was 67.7%, and cause specific survival was 86.9% for the 485 patients with curative treatment. 63.3% of them had their larynx preserved.

Conclusion: TLS was the most important single treatment modality in this series. Surgery as the main therapeutical approach (in combination with postoperative radiotherapy for advanced stages) leads to excellent survival rates and a high percentage of final organ preservation.

1150 ORAL

The role of postoperative radiotherapy in the treatment of salivary gland carcinoma's

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Purpose: In a Dutch multicentric retrosp. study prognostic factors for local control in salivary gland carcinoma's treated with surgery +/− radiotherapy were studied.

Methods and Materials: Out of 568 patients 501 were treated with surgery, in 389 combined with postoperative radiotherapy (50–70 Gy, mean dose 62 Gy). In the surgery alone group oral cavity tumors and small, radically resected tumors prevaled. Patients were treated between 1985 and 1994. The parotid gland was involved in 59%, submandibular gland in 14%, oral cavity in 24% and 3% elsewhere. Tumorstage was 29% T_1, 47% T_2, 18% T_3 and 6% T_4; 87% N_0. Resection margins were radical in 37%, close in 20% and irradical in 40%, unknown in 3%.

Results: In a multivariate analysis, using Cox proportional hazard regression analysis, independent factors for local control were T-stage ($T_1 = T_2 > T_3, > T_4$; $p < 0.001$), anatomic site (oral cavity > parotid and submand. gland, > elsewhere; p = 0.009) and treatment modality. Actuarial local control after 8 yr was 80% for surgery alone and 92% for the combined modality (in which more advanced cases prevaled), $p < 0.001$. No dose response relation was shown. Bone invasion ($p < 0.001$) was an independent histologic factor; histologic type, resection resection margin, age and sex were not.

Conclusion: Postoperative radiotherapy improves local control, however small (<4 cm) tumors in the oral cavity, radically resected, may be treated with surgery alone (97% local control). A dose response relationship was not shown, however most patients were treated with ≥60 Gy. Local control was independent of histologic type.

1151 ORAL

Acoustic neuromas (AN) treated by fractionated stereotactic radiosurgery (FSR)

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Single fraction radiosurgery of AN is remarkable for high control but not infrequent incidence of facial and trigeminal neuropathy. Large tumors treated surgically often result in deafness, facial neuropathy. FSR was developed to maintain efficacy and minimize toxicity.

Described are 38 patients (pts) with 39 AN. Age range: 35 to 89 years (mean 60). 2000 Centigray (cGy) divided weekly dose 400 or 500 cGy was delivered. Volume ranged 0.1–32.0 cc (mean 6.9). 23 AN had diameters <3 cms (range 0.3–2.8, mean 1.6). 16 measured 3 cms or greater ranged 3.0–5.0 (mean 3.7).

All tumors were controlled. 14 smaller (61%) decreased in size. 9 showed cessation of growth. Radiographic follow up ranged 4–34 months (median 16.3). Clinical follow up was 5–37 months (median 27.1). 21 with pure tone audiometry, 2 improved, 18 remained stable and 1 worsened. One pt had transient facial weakness after treatment which resolved. 22 pts, 15 had improved balance, 7 were unchanged.

13 of 16 (81%) larger AN diminished in size. Remainder showed cessation of growth. Radiographic follow-up ranged 4–30 months (median 20.7). Clinical follow-up was 14–35 months (median 28.1). 11 pts with audiometry 2 improved, 8 were stable and 1 worsened. Of 15 symptomatic pts, 12 had improved balance, 2 were stable, 1 worsened. All were controlled. No pt developed 5th nerve symptoms after treatment, no pts required surgery for treatment failure. 1 pt had temporary 7th nerve palsy.

FSR offers a therapeutic approach producing high control rates while avoiding frequent morbidity.

1152 ORAL

Complications in the surgical treatment of carotid body paragangliomas

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Purpose: Carotid body paragangliomas are rare neoplasms and usually occur in the third to sixth decade of life. Complications of surgical resection are frequently related to encasement of neurovascular structures and require meticulous subadventitial dissection.

Method: Retrospectively we studied our results and complications.

Results: During the period 1971 to 1995, 34 paraganglioma caroticum tumors were treated in 20 female and 8 male patients. The mean age was 39 (range 11–68) years. Localisation and extension of the tumor was visualized with digital subtraction angiography (DSA) and since 1992 by CT angiography and MRI according to Shamblin. Resection could be performed in 27 patients. There was no perioperative mortality. The external carotid artery had to be sacrificed in 7 pts and the internal carotid artery had to be reconstructed in 3 pts. All these tumors were classified to Shamblin III. One pt had a transcient CVA. Cranial nerve injuries occurred in 7 pts, all with Shamblin II/III lesions. These were temporary and involved the facial (3),