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INFLUENCE OF G-CSF ON FLUDARABINE AND ARA-C METABOLISM IN AML BLASTS DURING THERAPY

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Comparison of fludarabine and ara-C metabolism *in vitro* in AML blasts taken before G-CSF infusion with those obtained from the same patient after G-CSF demonstrated a 2-10-fold increase in the accumulation rate of both active triphosphates, F-ara-ATP and ara-CTP. To evaluate the effect of G-CSF on F-ara-ATP and ara-CTP metabolism during therapy, we designed a clinical protocol that stipulated fludarabine infusion (30 mg/m^2 over 30 min) 4 hr prior to ara-C (2 g/m^2 over 4 hr) daily for 5 days. 24 hr after the first fludarabine/ara-C infusions, G-CSF (400 μg/m^2) was infused daily until recovery of counts. Comparison of F-ara-ATP accumulation rates in blasts before and after the first G-CSF infusion indicated an increased accumulation rate in 4/5 patients. The rate of ara-CTP accumulation, studied only after fludarabine infusion, was not enhanced further by G-CSF infusion. The enhanced F-ara-ATP accumulation exhibited both *in vitro* and *in vivo*, was associated with an increased clinical response rate to fludarabine, ara-C and G-CSF therapy.

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CLINICAL PHARMACODYNAMICS OF 5FU. SIGNIFICANT RELATIONSHIP BETWEEN RESPONSE TO TREATMENT AND SYSTEMIC DOSE INTENSITY

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We have previously demonstrated the usefulness of 5FU adaptative control for reducing treatment side effects (Br J Cancer, 1989, 59: 287-290). We have now analyzed the hypothetical link between 5FU systemic dose intensity (AUC) and response in a large set of patients. One hundred and fifty head and neck cancer patients (35 stage II and 115 stage III-IV, mean age 61 yrs) were all treated by first line chemotherapy consisting of 3 cycles of cisplatin (100 mg/m^2 D1) and 5-day continuous venous infusion of 5FU (1 g/m^2/d D2 to 6 with adaptative control at D3). The AUC was determined (HPLC method) at each cycle and mean AUC (mAUC) calculated for the 3 cycles for each patient. Median survival was 2 yrs (range 2-56 months). mAUC varied between 15,300 and 47,000 ng/ml.h (average = 28,140). Response to treatment was CR 32 %, PR 45 % and NR 23%. There was a significant relationship (p = 0.001) between the intensity of the response and the increase in mAUC values. Notably, mAUC value at 29,000 ng/ml.h was the best threshold for predicting overall survival (p = 4.10^{-4}) : median survival was 27 months for patients with mAUC > 29,000 and 19 months for those with mAUC < 29,000. Cox analysis for overall survival showed tumor staging (p < 10^{-3}) and mAUC (< or > 29,000, p = 5.10^{-3}) to be independent prognostic indicators. This study establishes for the first time that systemic dose intensity of 5FU is linked to tumoral response and significantly influences patient survival.

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5-FLUOROURACIL (5-FU) COMBINED WITH THE [6S]-STEREOISOMER OF FOLINIC ACID ([6S]-FA) FOR PATIENTS WITH ADVANCED COLORECTAL CARCINOMA (CRC).

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We carried out 2 phase I-II studies of 5-FU combined with the [6S]-FA given in high doses for pts with CRC. Treatment comprised 5-FU by IV infusion for 2 hours (the initial dose was 350 mg/m2/d; it was incremented by 25 mg/m2/d until a maximal dose of 550 mg/m2/d) and [6S]-FA (100 mg/m2/d by rapid IV injection in Regimen 1, and 100 mg/m2 by rapid IV injection followed by a 2-hour infusion of 250 mg/m2 in Regimen 2) for 5 days, every 21 days. Twenty-five pts and 27 pts were assessed in Regimen 1 and in Regimen 2, respectively. They had had no prior chemotherapy. For pts treated with Regimen 1, the response rate (RR) was 52% (CR, 12%; PR, 40%). The median time to disease progression (TTDP) was 9.2 months. Survival at 12 months was 73%. For pts treated with Regimen 2, the RR was 37% (CR, 7%; PR, 30%). Median TTDP was 8.9 months. Survival at 12 months was 67%. Improvement in quality of life was achieved in most patients. The dose-limiting toxic effects (WHO grades ≥ 3) were diarrhea, dermatitis, and mucositis. One single episode of grade 4 diarrhea occurred. The [6S]-form of FA potentiates the antitumor effect of 5-FU given concomitantly. However, increase of the daily dose of the folate did not result in a therapeutic improvement.

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THE CONCEPT OF DOSE INTENSITY IN NEOADJUVANT CHEMOTHERAPY FOR HEAD AND NECK CANCERS : A PHARMACOKINETIC STUDY OF 90 PATIENTS

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In order to study the concept of dose intensity of 5 Fluorouracile ((FU) and Cisplatinum (CDDP) in head and neck cancers, it was looked for a relation-ship between individual pharmacokinetic parameters of 5 FU and CDDP an the response to the treatment.

90 patients were treated every 3 weeks. 1g/m^2/24 h of 5 FU was administered by continuous infusion for 96 h. 25 mg/m^2/d of CDDP were administered by 1 hour infusion for 4 days. The efficacy of the treatment was evaluated after 2 courses.

Plasma assays were performed every day of each course at 8 a : m and 8 p.m. 5 FU plasma levels were measured by liquid chromatography and free and total platinum were measured by inductively coupled plasma mass spectrometry. 55 objective responses (O.R.) (5 complete and 50 partial) and 35 no responses (NR) were observed.

The pharmacokinetic parameters : 5 FU and platinum plasma levels, areas under the curves were compared according to the response to the treatment. There was no difference between O.R (55) and NR (35).

So increasing the dose of 5 FU and CDDP does not seem to be able to lead to better therapeutic results and other approaches, for example weekly regimens, are needed.

First course	DAY1		DAY 2		DAY 3		DAY 4	
Plasma levels	8 a :m	8 p : m	8 a :m	8 p : m	8 a :m	8 p : m	8 a :m	8 p : m
OR (55) 5 FU ng/l	271	289	285	367	316	365	385	333
NR (35)	267	306	295	375	379	433	358	334
t.test p	0,65	0,7	0,68	0,84	0,59	0,08	0,32	0,99
OR (55) Platinum ng/l	0	353	304	608	562	859	755	1086
NR(35)	0	310	291	625	552	848	774	1071
t.test p		0,07	0,58	0,68	0,78	0,84	0,74	0,83

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FULL DOSE OXALIPLATIN (L-OHP) IN 49 PATIENTS (PTS) WITH RENAL FUNCTION IMPAIRMENT (RFI). S. Brienza*, J. Gastiaburu*, X. Grison, S. Lecouturier*, M. Ferreres, M. Itzhaki, E. Cvitkovic and J.L. Misset. SMST - Hôp Paul-Brousse, Villejuif - France. * Debiopharm, Lausanne - Switzerland.

Full dose Cisplatin (CDDP) is contraindicated in pts with RFI. CBDCA needs dose reduction to avoid increased toxicity (TX). L-OHP is a non hematotoxic active platinum salt without renal TX. As of 10/92 we treated 49 consecutive RFI pts with L-OHP. They are 20 men/29 women, median (m) age 60 (37-79), PS O=9, 1 =21, 2=16, 3=3 ; 11 pts were previously untreated, 18 had one previous CT, 20 had > 2 CT ; DX was 22 ovary, 11 urothelial, 10 colon, 3 NHL, 3 others ; 30 pts (60%) received previous CDDP, m: 510mg/m2 (55-1020mg/m2), 9 had CBDCA, m: 900mg/m2 (350-1570/m2). RFI cause was: previous CDDP 23, disease 21, post RT 4, unknown 2. The pre L-OHP plasma creatinine level (PCRL) was (m) 1.6 x N (normal upper value) (1.1-5.3xN), calculated creatinine clearance (m) 33ml/min (12-65ml/mn). L-OHP was given in 31 pts as single agent, 18 pts in combination ; as 2-6 hours IV in 36 pts, as 4-5 day chronomodulated 12h infusion in 13 pts. The dose/m2/cycle was < 80mg in 10 pts, 100mg/m2 in 19 pts, 120-135mg/m2 in 20 pts. The m: nb/cy/pt was 4 (1-27), with 17 pts having > 6 cycles. Total L-OHP dose was m: 400mg/m2 (67-2675mg/m2), 16 pts having > 600mg/m2. Max TX (WHO): Anemia gr III-IV in 3 pts, gr III thrombopenia in 3 pts, neurotoxicity (dysesthesias) gr II-III in 8 pts ; m : L-OHP dose 1000mg/m2 (300-2750), RFI increased in 5 pts, 4 of them due to the disease.

L-OHP is the platinum compound of choice in RFI, without increased TX despite full dose administration.

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INTRA-ARTERIAL (IAH) CISPLATIN FOR THE TREATMENT OF LIVER MALIGNANCIES -PHARMACOKINETICS AND PHARMACODYNAMICS

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The pharmacokinetics of cisplatin (cDDP) was examined after 11 intra-arterial hepatic route (IAH) and 34 intravenous (IV) treatments. IAH treatment was prescribed to patients with primary or metastatic liver carcinoma. cDDP was given in a dose range of 25-80 mg/m^2 per treatment with a time interval of 3-4 weeks between courses. IAH mannitol pretreatment was given to enhance drug uptake by the target organ in the first path and to achieve diuretic effect for the reduction of system toxicity. The peak Pt concentration in plasma at the termination of cDDP infusion (Time 0) correlated well with the dose of cDDP given for both IAH and IV administration and the mean peak Pt concentrations normalized to 35 mg/m^2 were 1.39±0.65 μg/ml and 3.96±0.98 μg/ml respectively (p<0.001). In both forms of drug administration similar bi-exponential pharmacokinetics were recorded but the rate of clearance was significantly different. More than 90% of the circulating cDDP derivatives were found to bind to proteins within the first 2 hours following drug administration. The unbound cDDP level was found to be most significant considering cDDP cytotoxicity as assayed in cell cultures. Our findings suggest that the first pass extraction of IAH cDDP increase exposure of the liver to the drug with a significant reduction of its systemic level. Patients receiving IAH cDDP treatment had only mild manifestations of the acute side effects typical to the IV treatment. No nephrotoxicity or neurotoxocity were observed in the IAH group.

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