1487 PUBLICATION

Phase II evaluation of oxaliplatin (LOHP) and Lyposomal doxorubicin (PLD) as salvage chemotherapy in advanced solid tumors

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Objectives: In a previous phase I study (Anticancer drugs 2003; 14: 633–8) we found the maximally tolerated dose of Oxaliplatin (LOHP) combined with fixed doses of stealth pegylated liposomal doxorubicin (PLD). With this combination, we observed an overall response rate of 55% in heavily treated patients with recurrent ovarian cancer. As both drugs have been shown to be very active in a variety of solid tumors, we performed an extended phase II study, using this drug combination in advanced tumors pre-treated with chemotherapy.
Patients and methods: Utilizing a Simon's optimal two-stage design, 54 patients with metastatic tumors (ovarian 56%, breast 24%, miscellaneous 20%), recurrent after treatment with 1 (13%), 2 (33%), 3 or more (54%) lines of chemotherapy were entered into the trial. Patients had a median age of 61 years (range, 41/81). Metastatic sites: peritoneum 38%, liver 24%, bone 20%, lung 10%, nodes 8%. Treatment was as follows: PLD 40 mg/m^2 over 40 minutes, LOHP 120 mg/m^2 over 2 hours. Both drugs were administered day 1, every 3 weeks. In order to prevent peripheral neuropathy and palmar-plantar erythrodysesthesia (PPE) the administration of drugs was preceded by the infusion of reduced glutathione, potassium and magnesium and, concomitantly with the infusion of PLD, upper and lower extremities were refrigerated.
Results: The 54 patients received 355 courses of chemotherapy (mean 6.5). Toxicity (WHO) in % of patients. Anemia G 1–2 (42%), neutropenia G 1–2 (45%), G 3 (15%), G4 (4%), (PPE) G 1–2 (48%), G 3 (7%). Amongst 54 evaluable patients, we observed an overall response rate (RR) of 59.2% (95% confidence interval, 45% to 72%). With a median follow-up of 17 months (range, 4–46) median time to progression (TTP) was 9.6 months (m), while median overall survival (OS) was 18 months. RR, TTP and OS for disease sites were as follows: ovary: RR 58%, TTP 9.6 m, OS 22.2 m; breast – RR 58%, TTP 8.1 m, OS not reached; miscellaneous: RR 63%, TTP 7.2 m, OS 9.8m.
Conclusions: A combination of PLD and LOHP administered with the above described procedure, has a manageable toxicity profile and can be safely given as outpatient chemotherapy for heavily pre-treated patients with relapsed tumors. A very promising anti-tumour activity was observed, not only in ovarian cancer, but in all other tumor types.

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Photochemical internalization of chemotherapeutic agents to circumvent multidrug resistance

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Multidrug resistance is the major confounding factor in solid tumour therapy. A novel way of circumventing resistance, in order to deliver higher levels of chemotherapy and hence increase efficacy, is photochemical internalization (PCI) of chemotherapeutic agents. PCI involves the co-administration of a photosensitizing compound that upon light activation induces the release of organelle-bound chemotherapeutic agents into the cancer cell cytoplasm. In this work, hypericin was used as the photosensitizing agent.
We aimed to determine firstly the relative effect of hypericin-induced phototoxicity on resistant bladder and breast cancer cell lines; and secondly to examine whether PCI using hypericin was able to potentiate the cytotoxicity of the chemotherapeutic drug mitoxantrone (MTZ) on the same cancer cells.
Bladder and breast cancer cells (MGHU1 and MCF7) and their resistant counterparts (MGHU1R and MCF7R) were exposed to increasing doses of MTZ or hypericin alone at incubation times up to 24 h, with and without blue light exposure at c. 400 nm, to determine appropriate doses for further PCI combination experiments. Cell viability was assessed by the MTT assay. MTZ alone (2 μg/ml) resulted in 60–85% cell killing in parental sensitive cell lines, with resistant cells exhibiting 3.5–11 times less cytotoxicity. Using hypericin, in the absence of MTZ, the sensitive and resistant cells lines exhibited no differential cytotoxicity following light exposure.
For PCI, hypericin doses (0.1, 0.2 μM) and light exposures were chosen that induced no significant cytotoxicity. In combination, the co-administration of hypericin (plus light exposure) with MTZ significantly increased the killing effect on multidrug resistant cancer cells, compared to MTZ alone ($p < 0.05$ for MGHU1R; $p < 0.05$ for MCF7R).
Our results are consistent with an additive or synergistic effect of the combined strategies. However, further investigations are warranted for elucidating the underlying molecular mechanisms.

1489 PUBLICATION

Determination of optimal times of delivery for improved acute tolerability of 5-fluorouracil, oxaliplatin and carboplatin in colorectal or lung cancer patients

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Background: Preclinical data have indicated that best tolerability resulted from dosing 5-fluorouracil (5-FU) during the rest span for and oxaliplatin (l-OHP) or carboplatin (CBDCA) 12 h apart. Chronomodulated infusion (chrono) based on these principles were better tolerated than constant rate infusion in cancer patients (pts).
Methods: The relevance of peak time of chrono delivery for tolerability was investigated in pts with advanced or metastatic colorectal or lung cancer treated with 5-FU-leucovorin (LV) and l-OHP or CBDCA. The drugs were infused according to a sinusoidally-varying infusion rate over 11.5 h for 4 days every 2 weeks. The delivery peak time of 5-FU-LV (700/850 - 300 mg/m^2/d) and that of l-OHP (25 mg/m^2/d) or CBDCA (50 mg/m^2/d) occurred 12 h apart. In Trials 1 & 2, 8 chrono schedules with peak times of drug delivery staggered by 3 h were tested in 114 previously-treated colorectal cancer pts; the main endpoint was the incidence of grade 3–4 toxicity over the initial 2 courses. In Trial 3, this endpoint was investigated in lung cancer pts randomized to receive one of 3 delivery schedules of chrono 5-FU-LV-CBDCA with times of peak delivery 8 h apart. The data of Trial 1 served to compute the optimal peak times of delivery of 5-FU-LV and l-OHP and their respective 90% confidence limits, using the bootstrap method. The data of Trials 2 and 3 were examined as validating sets.
Results: In Trial 1, chrono 5-FU-LV with a peak at 01:00 or 04:00 and l-OHP with a peak at 13:00 or 16:00 produced grade 3–4 toxicity in 16.7% vs 80% of the pts with peak delivery 12 h apart. Diarrhea, the main toxic effect, had a similar schedule-dependent pattern. The optimal peak times of chronomodulated infusion [90% Confidence Limits] were 03:57 [23:30 to 09:36] for 5-FU-LV and 15:57 [11:30 to 21:36] for l-OHP. This optimal time was confirmed in Trial 2 for colorectal cancer pts and in Trial 3 for lung cancer pts, with grade 3–4 neutropenia as main toxicity (7% vs 24%, $p = 0.047$). Tolerability was twice as good and optimal time window appeared to be narrower in men vs women.
Conclusions: This first time-finding study has identified an optimal time and its 90% CL for three widely used anticancer agents in cancer patients supporting the predictive value of preclinical models of chronotolerance. This trial design method is undergoing further validation for other agents in the Chronotherapy Group of the European Organisation for Research and Treatment of Cancer.

1490 PUBLICATION

Induction of Fas-L and down-regulation of tubulin are responsible for the cytotoxicity of apicularen A in HM7 colon cancer cell

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Apicularen A, a novel highly cytotoxic metabolite from the *myxobacterial genus chondromyces*, have been shown previously to cause growth inhibition in several types of cancer cell lines, and apoptosis in RAW 264.7
To determine the mechanism of cytotoxicity of apicularen A in colon cancer cell, effects of apicularen A on the cell growth and apoptosis-related molecules were examined in HM7 cells. Upon treatment with apicularen A, a time and dose dependent inhibition of cell growth was observed and this inhibition could be partially rescued by caspase-3 and pan-caspase inhibitor. Flow cytometric analysis showed that apicularen A caused cells to accumulate in sub-G_0/G_1phase. Although apicularen A induced DNA fragmentation, release of cytocrome c, translocation of AIF to nucleus, change of Bcl-2 and Bcl-X_L were not detected. The activation of caspase-3 was associated with caspase-8 activity and not with caspase-9. Apicularen A-induced apoptosis through a membrane-mediated mechanism was supported by up-regulation of Fas-L, but not Fas (CD95/APO-1). Total and polymerized β-tubulin amount, and mRNA level of β-tubulin were decreased, but *in vitro* polymerization of tubulin were not effected by apicularen A. Concurrently, immunofluorescence microscopy indicated that apicularen A treatment disrupted microtubule architectures and decreased density of microtubule, and cells had almost eccentric