1058 PUBLICATION

Phase I and pharmacokinetic study of irinotecan (CPT-11) given by 24 hours infusion plus oral uracil/tegafur (UFT) in patients with lung cancer

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We have previously reported that CPT-11 has time dependent antitumor activity and its combination with 5-fluorouracil (FU) in preclinical models suggested synergy between the two drugs. We also examined sequential effects of this combination, showing that the greater antitumor activity was obtained when CPT-11 was preceded by FU through enhanced inhibition of topoisomerase I enzyme unregulated by precedent FU effect (Pro. ASCO11: 308, 1992/Proc. ASCO12: 563, 1993). Since UFT appears to be mimic continuous infusion of FU, we used UFT in this study. This study was designed to determine the maximum-tolerated dose (MTD), dose-limiting toxicities (DLTs) and to evaluate the clinical efficacy of the CPT-11 and FU combination in patients (Pts) with advanced lung cancer. UFT 400 mg (twice daily) was given orally for consecutive 7 days followed by 24 hrs. iv infusion of CPT-11 (dose escalation: 100, 120, 140 and 160 mg/m^2, level 1 to 4) on day 8th every 2 weeks. 14 Pts (13 previously untreated NSCLC and I prior treated SCLC, median age 62, median PS 1, 10 males and 4 females) have received 59 courses of the treatment. MTD was defined as the dose level causing grade (G) 3–4 non-hematologic toxicities and/or G 4 hematologic toxicities in more than two-third of the Pts treated. MTD was reached at a dose level of 160 mg/m^2 of CPT-11. DLTs were considered as diarrhea and leukopenia. Three of 4 Pts given 160 mg/m^2 experienced G 3–4 diarrhea and/or leukopenia. Pharmacokinetic (PK) studies of CPT-11 and its active metabolite SN-38 were performed in 13 patients during first cycle. Total forms (lactone and carboxylate) of plasma CPT-11 and its active metabolite SN-38 were assayed using HPLC. No significant correlations were detected between CPT-11 and SN-38 in PK parameters (T.max, C.max and AUC). The recommended dose of CPT-11 for further combination phase II studies is 140 mg/m^2. 12 Pts were available for clinical responses and five out of 12 NSCLC Pts achieved PR (objective response rate was 42%). These results suggest that combination of CPT-11 and UFT may offer potential clinical benefits in the treatment of lung cancers.

Soft tissue & bone tumours

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Limb salvage (LS) by isolated limb perfusion (ILP) with TNF and melphalan (M) in 246 patients with advanced soft tissue sarcomas (STS): Results of 270 ILPS in 246 pts

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Objective: Achieve LS in pts with "irresectable/amputation" STS by ILP with TNF + M induction therapy for local control/limb sparing surgery.

Methods: 270 ILPs (TNF + M) in 246 pts: 1 ILP (222 pts) or 2 ILPs (24 pts). Very advanced tumors: recurrences in 45%, multiple tumors 22%, metastases in 15%; >10 cm in 46%. Grade III (66%). Previous XRT (13%), chemotherapy (15%). Resection of the tumor remnant usually (75%) done 2–4 months after ILP. **Independent review:** 2 independent committees, agreed in 80% of the cases (196 pts) that only ILP offered a chance for LS.

Results: major responses in 75% rendering tumors resectable in most cases. Clinical responses: CR (28%, pCR 28%), PR (47%), NC (17%), PD (6%), missing (1%). At median follow up >3 yrs limb salvage in 71% of the 196 patients considered justified ILP-cases by independent reviews. Little toxicity with no toxic deaths. Matched pair analysis with cases from the Scandinavian STS-database: TNF-ILP had no negative effect on survival (p = 0.96).

Conclusion: TNF-based ILP is a new and effective LS-option for advanced extremity STS. TNF destroys tumorvessels and increases intratumoral melphalan concentrations 4–5 fold in lab-models in Rotterdam, which explains the synergistic antitumor effects. TNF is now approved and registered in Europe for ILP of locally advanced grade 2–3 extremity STS.

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Synovial sarcoma: Experience of 150 cases in 11 years

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Purpose: Synovial sarcoma (SS) is known to be sensitive to chemotherapy (CT) but no large reviews include ifosfamide-based CT. This study aims to carry out a clinico-pathological correlation and identify prognostic features for SS.

Methods: Review of a prospective database adding retrospective information.

Results: 150 patients (pts) were assessed; median age was 30 years; median follow up was 52 months. 96 pts presented with primary disease, 26 with local recurrence (LR), 21 metastatic disease (MD) and 7 LR and MD. The site distribution was widespread with no relationship to large joints. Surgery was the first mode treatment in 75%, radiotherapy (RT) 14% and CT 6.7%. 61 pts had adjuvant RT. Histological subtypes were monophasic in 64, biphasic 69 and poorly differentiated in 17 with no influence on survival. Size trend, but not a cut-off of <5 cm vs >=5 cm, was a prognostic indicator (p < 0.001). The current AJCC Staging System defined prognosis less well than the recently proposed RMH Staging System [1]. LR rate with clear margins was 18% compared to 61% for involved margins (p < 0.001). Overall radiotherapy significantly reduced LR (p = 0.03). Pts with LR had a worse survival (p < 0.001). 80 pts had CT – in 55 pts CT was therapeutic with 12 of 20 pts having a partial response to a ifosfamide and doxorubicin regimen. 4 pts had complete response after CT. 21 pts had pulmonary metastasectomy with an actuarial 5 year survival of 23%. At final analysis 67 pts were disease free, 16 alive with disease and 67 had died. Actuarial 5 year survival rate was 57%.

Conclusions: SS tends to affect young people but has no specific relationship to large joints. Adequate surgical margins and RT gives the best local control and may affect survival. SS is often chemosensitive and given its poor prognosis multicentre trials of adjuvant therapy are warranted. Future improvements in survival will depend on better CT.

[1] Ramanthan RC et al. Modified Staging System for Extremity Soft Tissue Sarcomas. Ann Surg Oncol 1999; in print.

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Initial response to neoadjuvant chemotherapy combined with regional hyperthermia (RHT) in high-risk soft tissue sarcomas (HR-STS) of adults and its correlation to survival parameters

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This analysis was performed to evaluate response rate, time to progression and survival for neoadjuvant chemotherapy combined with RHT followed by surgical resection and radiation in patients (pts) with locally advanced primary or recurrent HR-STS.59 pts (31 primary/28 recurrent) eligible with HR-STS (tumor grade II/III, tumor size >8 cm and deep) were treated at KGMC. Preoperative chemotherapy consisted of adriamycin (50 mg/m^2) on day 1, etoposide (125 mg/m^2) on day 1 and 4, and ifosfamide (1250 mg/m^2) on days 1 to 4 (EIA). RHT was given (1 hr at 42°C) on days 1 and 4. After receiving 4 EIA-cycles plus RHT, pts then underwent surgical resection which was followed by radiotherapy. Clinical response rate (42%) evaluable in 52 pts included: 1 CR, 8 PR and 13 MR regressions. 17 pts showed SD and 13 pts PD. 49 pts underwent surgery and 40 pts were resectid without mutilation. In 6/49 resection specimens no viable tumor was present (6 pCR). During follow-up (median: 49 months) the 5-year overall survival (OS) is 46%. At present 28 pts are alive (median survival 76 months). Survival data of pts with initial tumor response (CR/pCR + PR/MR) differ significantly from non-responding patients (NC/PD). Based on these results in HR-STS, a randomized prospective phase III Intergroup study (EORTC 62961/ESHO RHT-95) is ongoing comparing neoadjuvant chemotherapy with and without RHT.