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Diabetes mellitus impairs the response of intra-arterial chemotherapy in hepatocellular carcinoma

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Background: Diabetes mellitus has been associated with poorer outcome in patients with hepatocellular carcinoma, but the influence of diabetic conditions on chemotherapy remains uncertain. Intra-arterial chemotherapy is one of the treatment modalities for advanced hepatocellular carcinoma. The study compares the response of intra-arterial chemotherapy on diabetic or non-diabetic patients with advanced hepatocellular carcinoma.
Material and Methods: Between August 2007 and May 2008, 52 patients with unresectable advanced hepatocellular carcinoma underwent intra-arterial chemotherapy with cisplatin and fluorouracil. Tumor response was assessed by computed tomography or magnetic resonance imaging. *In vitro*, hepatocellular carcinoma cell line Hep G2 was evaluated for cytotoixc effect of cisplatin and fluorouracil in different concentrations of insulin and glucose mimicking diabetic conditions.
Results: Among the 52 patients, 14 were diabetic while 38 were non-diabetic. The partial response rate was similar in the two groups (14% in diabetics and 18% in non-diabetics). Non-diabetic patients had a lower rate of progressive disease (16% vs 43%, $p = 0.039$). The median time to disease progression was found to be significantly longer in non-diabetics compared with the diabetic counterpart (a median of 206 days vs 88 days, $p = 0.02$). The proliferation of hepatocellular carcinoma cell line Hep G2 cells was promoted in the increasing concentration of insulin from normal physiological concentration, 0.0005 mg/L to hyperinsulinemia status, 5 mg/L. In the presence of chemotherapy agents, cisplatin and fluorouracil, Hep G2 cells showed less cytotoxic effect while treated with higher concentrations of insulin. On the other hand, the proliferation of Hep G2 cells was not influenced significantly by different concentrations of glucose even in the conditions with cisplatin or fluorouracil.
Conclusions: Our study showed that intra-hepatic chemotherapy for unresectable hepatocellular carcinoma was less effective in diabetic patients than non-diabetic counterpart in terms of progression free rate and time to disease progression survival. Insulin, rather than glucose, stimulated hepatocellular carcinoma cells, Hep G2, to proliferate rapidly and enhanced the resistance to chemotherapeutic agents, cisplatin and fluorouracil. These results emphasize the important role of diabetes mellitus in chemotherapy treatment of advanced hepatocellular carcinoma.

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Hepatocellular carcinoma presenting with lung metastasis: clinical characteristics and prognostic factors

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Background: The efficacy of systemic chemotherapy for hepatocellular carcinoma (HCC) has been limited, but sorafenib has changed the strategy treating for metastatic HCC. The lung is one of the most common metastatic sites for HCC. Therefore, we focused on clinical features and prognostic factors of HCC patients (pts) with lung metastasis in this study.
Methods: Between January 2000 and April 2008, 1,117 HCC pts were admitted into our division. During this period, extrahepatic metastasis was detected in 278 pts, and the initial metastatic site was lung in 130 pts. The relationships between the characteristics of these pts at the time of lung metastasis detection and prognosis were examined.
Results: There were 106 males and 24 females. Median age was 64 years. The Child-Pugh classification was A in 92 pts, B in 37 pts. HCV Ab was positive in 57 pts, HBs Ag was positive in 46 pts, and both were negative in 27 pts. The median survival time of all pts was 286 days. Univariate analysis revealed 15 of the 21 variables evaluated to be significantly associated with survival time: sex, number of lung metastasis, presence of intrahepatic HCC, maximum size of intrahepatic HCC, presence of tumor thrombus, AFP, PIVKA II, albumin, prothrombin time, ALP, hemoglobin, presence of ascites, Child-Pugh classification, previous systemic chemotherapy and previous history of hepatic resection. Multivariate analysis using the Cox proportional hazards model demonstrated a lower number (<5) of lung metastases ($p < 0.0001$), the systemic chemotherapy after lung metastasis ($p = 0.0005$), the absence of ascites ($p = 0.0008$), the absence of intrahepatic HCC ($p = 0.0050$), AFP (<2000) ($p = 0.0069$), and absence of tumor thrombus ($p = 0.0295$) to be independent favorable prognostic factors.
Conclusions: These results may provide useful reference data for determining treatment strategies and planning further clinical trials involving HCC patients with lung metastasis.

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Hepatocellular carcinoma: a retrospective analysis of 276 cases

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Background & Objective: This study aimed at documenting the spectrum of clinicopathological variations in hepatocellular carcinoma (HCC).
Design: It was a retrospective study.
Place and Duration of Study: This study was conducted at the Institute of Nuclear Medicine and Oncology (INMOL) Hospital, Lahore, Pakistan from March 1997 to July 2008.
Materials & Methods: The profiles of 276 patients with a biopsy proven hepatocellular carcinoma were analyzed in this period. The data collected was age, sex, clinical presentation and laboratory investigations including liver function tests, alpha fetoprotein and hepatitis profile.
Results: Weight loss, jaundice and right upper quadrant abdominal pain were the main presenting symptoms. Out of 276 patients, alpha fetoprotein values were raised in 201 (72.83%) patients. 165 (59.78%) patients were found to have or have had HBV (hepatitis B virus) and 211 (76.45%) patients were anti-HCV (hepatitis C virus) positive. 193 (69.93%) patients were cirrhotic. History of alcohol abuse was found in 9 patients.
Conclusion: The common association of HCC with cirrhosis and hepatitis B and C suggests that vaccination against HBV on nationwide basis can decrease prevalence of this malignancy. There is a need to generate public awareness regarding the transmission of these viruses. Early diagnosis and intervention is also important to the successful management of HCC.

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Investigation of the efficacy on transcatheter arterial chemoembolization combined with or without Chinese herbal therapy for hepatocellular carcinoma: meta-analysis

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Background: In recent years, there has been a great interest in complementary and alternative treatment for cancer. Traditional Chinese medicine (TCM) is sometimes used in conjunction with transcatheter arterial chemoembolization (TACE) for the treatment of HCC in Asian countries. The main objective of this study is to systemically review the efficacy of TCM therapy in hepatocellular carcinoma (HCC) patients receiving TACE.
Materials and Methods: Meta-analysis was performed for randomized controlled trials (RCTs) comparing TCM administration *versus* no TCM treatment given to HCC patients receiving TACE. Overall survival and tumor response were the primary end points. English and non-English publications in ten electronic databases (CNKI, VIP, CDSR, EMBASE, EMDP, MEDLINE, CAB Abstracts, EBM Reviews, AMED, and CINAHL) were extensively searched from 1910 to February 2009. Two review authors assessed trial quality and extracted data independently. The method used for this systematic review followed the Quality of Reporting of Meta-analyses guidelines.
Results: Thirty RCTs involving 2428 HCC patients treated with TACE were included. Treatment with TCM was associated with a significant rise in the number of patients with survival >1-year (odds ratio (OR) 1.92, 95% confidence interval 1.43 to 2.57), survival >2-year (OR 3.55, 2.36 to 5.36), and survival >3-year (OR 5.12, 2.76 to 9.52), a significant rise in the number of patients reported complete or partial response (OR 1.87, 1.53 to 2.28) and non-deterioration performance status (OR 3.78, 2.58 to 5.55), a significant increase in $CD3^+$ T cell level (weighted mean difference (WMD) 13.80, 95% confidence interval 11.86 to 15.73), $CD4^+$ T cell level (WMD 4.54, 2.19 to 6.89), and natural killer cell level (WMD 7.77, 4.30 to 11.24), a significant lower blood alpha-fetoprotein concentration (WMD 131.27, 86.58 to 175.96), a significant increase in white blood cell count (WMD −1.85, −2.88 to −0.82), a significant lower risk in patients with grade 2−4 nausea and vomiting (OR 0.24, 0.10 to 0.57), and a significant rise in patients with increased or stable body weight (OR 3.75, 1.48 to 9.49).
Conclusions: The evidence from this review supports the use of TCM to enhance the efficacy of TACE in HCC patients. Funnel plots have demonstrated no publication bias for the meta-analyses of primary

outcomes. However, owing to limited data and heterogeneity of the included studies, further RCTs are required to pursue.

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Exposure-response analysis to identify abt-869 dose in hepatocellular carcinoma (HCC) patients

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Background: ABT-869 is an orally bioavailable, potent and specific inhibitor of all VEGF and PDGF family receptor tyrosine kinases. The objective of this analysis was to identify ABT-869 dose/dosing regimen for a potential phase-3 study in HCC patients.
Methods: An exposure-response (safety/efficacy) analysis was performed for patients (pts) enrolled in a phase 1 (multiple types of solid tumors) and 3 phase 2 monotherapy studies (non-small cell lung cancer (NSCLC), HCC and renal cell carcinoma (RCC)). Studies were conducted internationally in advanced/metastatic solid tumor pts to characterize ABT-869 efficacy/safety profile. Pts received ABT-869 until progressive disease or intolerable toxicity across all studies. Efficacy was assessed by RECIST criteria; safety by NCI-CTCAE, v3.0 and dose/dosing regimen was selected based on acceptable safety/efficacy responses. For drug exposure, plasma concentrations were fitted to a 1-compartmental model by the nonlinear mixed effects modeling (NONMEM) approach and various demographic covariates were tested. Trial abbreviation/registry numbers: Phase 2 trial of ABT-869 in HCC (NCT00517920); ABT-869 in subjects with NSCLC (NCT00716534); ABT-869 in Advanced RCC, after Sunitinib Failure (NCT00486538). All trials: ongoing; not recruiting; sponsored by Abbott Laboratories. ABT 869 is being developed in collaboration with Genentech.
Results: Among 224 pts in the analysis, 45% were Asian, 47% Caucasian and 8% other races; mean body weight was 72 kg (range 35–177 kg). Approximately 95% of pts received drug based on body-weight (mg/kg) while remaining pts had fixed dosing (mg). ABT-869 exposure was significantly ($p < 0.05$) associated with increased hypertension (HT) and skin toxicity events. Under weight-based dosing scheme, heavier pts had greater risk of toxicity as the exposure increased significantly. Transitioning from 0.25 mg/kg weight-based to 17.5 mg fixed dosing, exposure-safety response analysis showed that the predicted HT rate remains similar (33%) for pts with averaged body weight; however in pts with lower and higher body weights, the HT rate range is tighter for the fixed dose (30−36%) as compared to weight-based dose (23−44%). A similar trend was observed for skin toxicity. The model predicted the HT rate for HCC patients successfully and showed lower variability across patients for fixed dose.
Conclusions: A fixed 17.5 mg dose of ABT-869 is recommended for HCC patients based on the exposure predicted safety profile.

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Clinical features of hepatocellular carcinoma patients underwent resection after concurrent chemoradiotherapy

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Background: This study was to examine the clinical features of the patients who underwent hepatic resection after receiving concurrent chemoradiotherapy.
Materials and Methods: From January 2000 to October 2007, one hundred fifty six patients with hepatocellular carcinoma received concurrent chemoradiotherapy, and those patients who underwent hepatic resection on the primary site during follow-ups were 14 (9%). Most patients were received 45 Gy with the fraction size of 1.8 Gy and 2 patients treated with 43.2 Gy. The chemotherapy was administered by intra-arterial infusion with 5-FU and 3−12 cycles of chemotherapy were performed after the radiotherapy. The tumor size before the concurrent chemoradiotherapy was 5−20 cm and the mean value was 10.4 cm. In radiological examinations, the disease status before the operation was shown to be 2 complete remissions, 6 partial remissions and 4 stable diseases. Two cases showed the suspicious recurrence from imaging studies.
Results: The hepatic resections were performed between 1 month and 21 months after concurrent chemoradiotherapy. A lobectomy was performed in most of the patients (13), and a bisegmentectomy was performed in the remaining 1 patient. In pathological findings, the ratios of necrosis were 5% to 100%. Four patients showed total necrosis and 12 patients (85.7%) showed the ratios of necrosis of 70% or higher. The resection margins were close to the tumor in 5 patients and 1 patient showed positive tumor resection margin. There were vessel invasions in 6 patients and capsular invasions in 5 patients. The median overall survival time was 28 months and the median disease free survival time was 19 months. The number of patients who were disease free after the operation was 3 (21.4%), and the number of patients with intrahepatic metastasis was 6 (42.9%) and distant metastasis was 5 (35.7%). Findings of vessel infiltration and capsule infiltration in univariate analyses were significant for survival rates ($p = 0.006$, 0.043), and disease free survival rates ($p = 0.014$, 0.004). In multivariate analyses, vessel infiltration was a significant factor for survival rates ($p = 0.01$), and capsule infiltration was a significant factor for disease free survival rates ($p = 0.01$).
Conclusions: Unresectable hepatocellular carcinoma could be resectable after concurrent chemoradiotherapy in selected patients. However, more clinical cases and prospective studies are necessary.

6615 POSTER

Advanced biliary tract cancer in Peruvian population

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Background: Biliary tract cancer (BTC) is not common cancer, but there are high incidence in some areas of Latin America and Asia, BTC includes intrahepatic cholangiocarcinoma, Klastkin tumor, extrahepatic cholangiocarcinoma, gall bladder cancer, and ampulla of Vater cancer. The standard treatment has not been established at the moment, traditional chemotherapy (5FU-based) has shown minimal activity and does not prolong survival, and each cancer has different responsiveness to anti-cancer treatment. We evaluated 178 patients (pts) with advanced biliary tract cancer.
Methods: Retrospective reviewed 178 BTC pts between (2000–2005).
Results: 178 pts (112 female, 42 male) were evaluated, median age 60 (range 16−91), median karnofsky performance status 70%. 151 cases (84%) were associated with gallstones, only 1 case present polyps. The clinical feature present most frequently was abdominal pain 81.5% (145 pts), weight loss 48.8% (87 pts), jaundice 43.3% (77 pts), mass in the right upper quadrant 36.5% (65 pts), itching 5.1% (9 pts), anorexia 19.7% (35 pts).
Primary tumor sites were gallbladder (38%), extrahepatic bile duct (29%), intrahepatic bile duct (9%), ampulla of Vater (2%), not specified (22%).
Predominant localizations of metastases were liver 70%, others 30% (lymph nodes, peritoneum).
Only 13.5% (24 pts) received chemotherapy using 5-FU-based chemotherapy the rest received best medical support. The patients that recived chemotherapy had median survival of 4.1 months and the patients that only recived best support had 3.4 months of median survival.
Conclusions: Our analysis showed that in BTC, gallbladder cancer is most common with predominant liver metastases and clinical features similar to previous published articles, treatment with chemotherapy produced modest benefit in survival.

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Serial alpha-fetoprotein evaluation and survival in hepatocellular carcinoma patients treated with sorafenib

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Background: There is poor correlation between conventional radiologic response criteria and treatment outcomes of patients with advanced hepatocellular carcinoma (HCC). The prognostic value of serial α-fetoprotein (AFP) measurement has not been assessed in HCC patients receing sorafenib. Aim of this study was to examine AFP trends as a surrogate endpoint for survival.
Patients and Methods: Serum AFP was prospectively collected at baseline and during treatment, in conjunction with radiological assessment. In patients with increased AFP levels ($\geqslant$8 U/mL) at baseline, we defined AFP response as a decrease $\geqslant$20% in AFP value after 8 weeks from start of sorafenib treatment. Kaplan-Meier plots were constructed for progression-free survival (PFS) and overall survival (OS), and compared with the Log rank test to evaluate the correlation with AFP response.
Results: Overall 129 patients were evaluated, of which 21 had normal baseline AFP levels, remaining stable throughout treatment course. Median PFS and OS were longer in AFP responders than in non-responders: