9076 POSTER

Purine analogs sensitize the multidrug resistant cell line (NCI-H460/R) to doxorubicin

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Multidrug resistance (MDR) is a significant factor that limits the efficacy of classic chemotherapeutics in lung cancer. We used the resistant cell line NCI-H460/R and its counterpart NCI-H460 to investigate the potential of purine analogs to overcome MDR. We observed that two purine analogs, sulfinosine (SF) and 8-Cl-cAMP, exerted dose dependent effects on cell growth of both parental and resistant cell lines. SF and 8-Cl-cAMP significantly decreased *mdr1* expression in NCI-H460/R cells. When a low concentration (1 μM) of SF and 8-Cl-cAMP was combined with doxorubicin (DOX), the drugs demonstrated synergistic growth inhibitiory effects in both cell lines. Pretreatment with SF and 8-Cl-cAMP improved the sensitivity to DOX more than verapamil (VER). The observed increased accumulation of DOX after the treatment with SF and 8-Cl-cAMP was consistent with results obtained with VER. Our results show that SF and 8-Cl-cAMP modulate MDR in NCI-H460/R, especially when applied before DOX administration. Along with the exhibited potential for MDR reversal, purine analogs in combination with DOX represent valuable agents with a potential for improving chemotherapy.

9077 POSTER

Phase 2 study of pemetrexed and cisplatin plus either enzastaurin or placebo in chemonaive patients with advanced NSCLC

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Background: Enzastaurin (ENZ), an oral serine/threonine kinase inhibitor, has the potential to be used in combination with chemotherapeutic agents. Previous clinical studies in combination with pemetrexed have shown additive antitumor activity (Nakajima et al, JCO 2006) and a tolerable safety profile (Hanauske et al, JCO 2006).
Materials and Methods: This study enrolled chemonaive patients (pts) with stage IIIb/IV NSCLC and performance status 0−1, and was conducted in two parts: Part 1 was an open-label safety lead-in, evaluating safety of 2 cohorts (Coh): Coh1 had ENZ 250 mg BID daily, while Coh2 had 500 mg BID, both in combination with 500 mg/m^2 pemetrexed and 75 mg/m^2 cisplatin (P/C) in a 3-week cycle. Part 2 was a multicenter, double-blind, randomized study comparing the combination of P/C with ENZ (500 mg daily) or placebo in nonsquamous NSCLC pts. Primary endpoint was PFS.
Results: Between 09/07 and 08/08 a total of 13 pts were enrolled in part 1 (9 in Coh1, 4 in Coh2). Only 22 pts were enrolled in part 2 because of early closure of the trial. All were Caucasian, 16 female, 19 male, mean age 59 yrs, 74% PS 1. Histology diagnosed as 77% adeno/8% large/15% squamous cell in part 1 and 64% adeno/23% large/14% NOS in part 2. In study part 1, one patient (Coh1) discontinued before completing cycle 1 due to a drug-related serious adverse event (SAE) (paralytic ileus) and was replaced. One patient in Coh2 discontinued due to a drug-related adverse event (myalgia). Overall 3 pts (23%) experienced a possibly drug-related SAE (paralytic ileus, increased blood amylase, pulmonary embolism), all in Coh 1. Best overall response was 8 PR (1 not confirmed), 2 SD and 2 PD. In part 2, one patient discontinued due to a drug-related adverse event (hypertension) in the ENZ arm. Two pts (9%) experienced at least one possibly drug-related SAE, both in the placebo arm (duodenal ulcer and candidiasis, tachyarrhytmia). The most common drug-related non-hematological CTC grade 3/4 toxicity was grade 3 myalgia (one in Coh1 and one in Coh2). The most common, expected CTC grade 3/4 lab toxicity was neutropenia (two in Coh1 and one in Coh2, and two in the placebo arm).
Conclusions: The combination regimen of ENZ and P/C was well tolerated. Although the combination treatment showed good activity in this study, the trial was closed early based on the interim analysis of two other pivotal NSCLC studies, which showed no improved outcome by adding ENZ to chemotherapy.
Study H6Q-MC-S021 sponsored by Eli Lilly

9078 POSTER

Subset analysis of a phase III trial comparing two platinum-based doublets: i.v./Oral vinorelbine (NVB) vs docetaxel (DTX): impact of histology on response and survival in advanced Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Histology gains predominance in scientific communications on NSCLC. Following a large phase III trial comparing two reference platinum-based doublets as first-line chemotherapy in advanced NSCLC, we performed a retrospective analysis in order to evaluate the impact of histology on the efficacy parameters.
Materials and Methods: From February 2004 to January 2006, 381 patients with unresectable or metastatic NSCLC from 42 investigational centers in 19 countries were randomly assigned and treated by either a cisplatin-based doublet with iv/oral NVB on day 1.8 (NVB Arm, 190 pts) or DTX on day 1 (DTX Arm, 191 pts), both combinations delivered every 3 weeks for a maximum of 6 cycles. Time to Treatment Failure (TTF) was the primary endpoint. Patients characteristics in both arms were balanced for age, sex, disease extent, and PS. Histological types at diagnosis in NVB/DTX arms (%): Squamous 65(34.2)/64(35.5); Adenocarcinoma (ADK) 79 (41.6)/75 (39.3); Large cell 8 (4.2)/18 (9.4); BAC 2 (1.1)/0 (0); Giant Cell 1 (0.5)/1 (0.5); Unknown 35 (18.4)/33 (17.3). An exploratory analysis on OR, TTF and OS was performed taking into account the Squamous, Adenocarcinoma and other histology of patients included in both arms.
Results: Overall, both arms reported similar results in terms of OR (NVB 27.4% [95% CI 21.2−34.2]; DTX 27.2% [95% CI 21−34.2]) (p = 0.97), TTF (NVB 3.22 months [95% CI 2.96−4.24]; DTX 4.11 months [95% CI 3.45−4.50]) (p = 0.20), and OS (NVB 9.9 months [95% CI 8.41−11.6]; DTX 9.8 months [95% CI 8.80−11.5]) (p = 0.58). OR (%) by histology (NVB/DTX): ADK 29.1/22.7; other 26.1/30.2. Considering ADK and Squamous, TTF and OS are reported in the following table:

	NVB Arm		DTX Arm	
	Squamous	Adenocarcinoma	Squamous	Adenocarcinoma
TTF (months)	3.22	3.05	4.22	3.94
95% CI	2.76−4.63	2.33−4.27	3.81−4.57	2.23−6.08
OS (months)	8.87	11.73	9.82	11.60
95% CI	6.44−12.81	8.67−16.46	8.41−12.19	9.72−15.74

Conclusion: Adenocarcinoma seems in relation with a better response to chemotherapy but it is not the only criterion that can determine on its own a therapeutic strategy. Third generation platinum-based doublets are effective in all histological subtypes of advanced NSCLC, as confirmed in this trial with NVBo + CDDP.

9079 POSTER

Pemetrexed in combination with cisplatin or carboplatin in the first line therapy of locally advanced or metastatic non-small cell lung cancer: a randomized, two-arm, parallel, open-label, multicentric phase 2 study

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Background: Pemetrexed (P) single agent has shown to be effective and safe in 2nd line treatment (Tx) and in combination with platinum compounds in 1st line Tx of patients (pts) with advanced non-small cell lung cancer (NSCLC). P single agent was approved for 2nd line Tx and, combined with cisplatin (Cis), 1st line for pts with other than predominantly squamous histology. This study H3E-SB-S109 evaluated P+Cis and P+carboplatin (Car) in 1st line Tx of stage IIIb/IV NSCLC.
Material and Methods: 130 pts with cytol./histol. confirmed NSCLC stage IIIb or IV were planned to be random. to P (500 mg/m^2)+Cis (75 mg/m^2) or P (500 mg/m^2)+Car (AUC6) d1 q3 wks, for up to 6 cycles. Primary outcome was 6 mo progression-free survival (PFS) rate [estimate based