135−150 mg/m^2 every 2 weeks (q2w) without vitamin supplementation (Krug, Clin Cancer Res 2003;9:2072−8). This phase 1 study evaluated the safety of higher pralatrexate doses with vitamin supplementation to minimize toxicities in pts with advanced NSCLC.
Materials and Methods: Pts age ⩾18y with stage IIIB or IV NSCLC received pralatrexate q2w in 4-wk cycles with folate and vitamin B_{12}. Outcomes in this report include adverse events, pharmacokinetics (PK), and investigator reports of treatment response.
Results: 39 pts were treated (23 female, 34 White, median age 62y [range, 40−77y]). The number of prior chemotherapy treatments was 1−2 in 20 pts and 3+ in 19 pts. Pts received a median of 2 pralatrexate cycles (range, 1−12). Rates of treatment-related grade 3−4 adverse events at any time were (doses ⩽ 190 mg/m^2, > 190 mg/m^2) stomatitis/mucosal inflammation (22%, 33%), fatigue (0%, 13%), and hand-foot syndrome, headache, increased ALT, back pain, dehydration, thrombocytopenia, and neutropenia (0%, 3% each). Treatment-related serious adverse event rates were 0% and 23% for doses ⩽ 190 and > 190 mg/m^2, respectively. The table summarizes dose-limiting toxicities (DLTs) during cycle 1 (cohorts in chronological order).

Dose, mg/m^2	Infusion duration, min	N	No. of Pts with DLT
150	3−5	1	
190	3−5	1	
230	3−5	1	
270	3−5	6	1 Mucositis (Gr3)
325	3−5	3	2 Mucositis (Gr3)
270	3−5	10	2 Mucositis (Gr3)
			1 Mucositis+fatigue (Gr3+3)
			1 Mucositis+fatigue+headache (Gr3+3+3)
			1 Hand-foot syndrome (Gr3)
			1 Elevated ALT+back pain (Gr3+3)
230	3−5	5	3 Mucositis (Gr2)
			1 Fatigue+hemorrhagic mucositis (Gr3+4)
230	60	5	1 Mucositis (Gr3)
			1 Mucositis+neutropenia (Gr2+3)
			1 Dyspnea (Gr3)
			1 Syncope+somnolence (Gr3+3)
190	3−5	2	2 Mucositis (Gr3)
190	60	5	1 Fatigue+dyspnea+mucositis (Gr3+3+2)

PK was dose-proportional and was not altered significantly by extending the infusion to 60 min. ORR by RECIST was 8% (3/39; 95% CI: 0.7%-16%), with 2 CR (22+ and 16+ months) and 1 PR (10 months). Disease control rate (CR, PR, or SD and TTP > 2 months) was 49% (95% CI: 33%-64%).
Conclusions: Pralatrexate in combination with vitamin B_{12} and folate was safe and active in pts with previously treated NSCLC, with durable CRs in this phase 1 trial. Mucositis remained the DLT. Pralatrexate 190 mg/m^2 with vitamin supplementation is being compared to erlotinib treatment in a randomized phase 2b trial (NCT00606502) in pts with previously treated NSCLC.

9087 POSTER

The feasibility of weekly paclitaxel in combination with carboplatin for advanced non-small cell lung cancer with idiopathic interstitial pneumonias: a pilot study

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Background: Idiopathic interstitial pneumonias (IIP) appear to be associated with lung carcinogenesis. In lung cancer combined with IIP, acute exacerbation of interstitial pneumonias (AE) frequently occurs after the anti-cancer treatments. The AE was fatal and poor prognostic factor of these patients. However, no current consensus and evidence on whether aggressive anti-cancer treatments, such a chemotherapy, for advanced stage non-small cell lung cancer (NSCLC) with IIP was regarded as a serious clinical problem. This study was conducted to elucidate cumulative incidence of AE in NSCLC with IIP who had received standard chemotherapy.
Patients and Method: Advanced NSCLC with IIP who had never received chemotherapy or radiotherapy from 2004 to 2008 at Nippon Medical School Main Hospital were enrolled. Patients received paclitaxel (PTX) 100 mg/m^2 weekly for 3 of 4 weeks and carboplatin (CBDCA) area under the curve (AUC) = 5 on day 1 of each 4-week cycle. The safety and efficacy of PTX plus CBDCA was prospectively investigated.
Results: Eighteen patients [male/female, 14/4; median age 71 years (38−81); performance status 0/1, 7/11] were enrolled. The 6 of 18 patients were diagnosed idiopathic pulmonary fibrosis (IPF). The median number of cycles administered per patients was 4 (range 1−7). The median progressive free survival was 27 weeks. The overall response rate was 61%. The median survival was 46 weeks, and 1-year survival rate was 22%. During the follow-up period, AE was observed in 5 of 18 patients (28%). Treatment-related AE occurred in only one patient (6%) with histological confirmed usual interstitial pneumonia (UIP). Other main adverse events were; 33% of Grade 3 or 4 neutropenia, 22% of Grade 2 neuropathy.
Conclusion: The safety and anti-tumor response of PTX combined with CBDCA for advanced NSCLC with IIP were well acceptable. These results suggest that the chemotherapy of PTX plus CBDCA is candidate of treatment for NSCLC with IIP. Further large-scale prospective study for NSCLS with IIP should be performed.

9088 POSTER

Phase III study of Lipoplatin plus Gemcitabine versus Cisplatin plus Gemcitabine in advanced NSCLC; interim analysis

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Background: Lipoplatin is a liposomal formulation of cisplatin, designed to reduce its adverse reactions without reducing efficacy. This is a report of an ongoing randomized, multicenter, non-inferiority phase III trial (LipoGem-PIII-1L, 0−218b/6th/23−3−05) comparing OS/response, safety and QOL of Lipoplatin versus cisplatin, both combined with gemcitabine against advanced stage NSCLC.
Materials and Methods: Interim analysis of 101 patients' safety and response data, emphasizing the correlation of results with the histological subtype of NSCLC. Sixty patients were assigned to Lipoplatin arm (LipoGem) and 41 patients were assigned to the cisplatin arm (CisGem). Patients received Lipoplatin 120 mg/m^2 D1, 8, 15 or cisplatin 100 mg/m^2 D1, combined with gemcitabine 1,000 mg/m^2 D1, 8, in 3-week cycles, with disease evaluation after 3 and 6 cycles (LipoGem and CisGem arms, respectively).
Results: Response: Evaluable patients were 52 in LipoGem arm and 32 in the CisGem arm. The study meets the noninferiority goals with a slight superiority of LipoGem over CisGem across all histological subtypes combined. However, among patients diagnosed with adenocarcinoma PR, SD and PD were 48%, 38% and 14% for LipoGem and 32%, 36% and 32% for CisGem arms, respectively. Toxicity: Nephrotoxicity grade III occurred in 8.5% in LipoGem arm versus 12.5% in CisGem arm, while respective values for nausea and vomiting grade III were 1.7% versus 10%, neurotoxicity grade III were 0 versus 2.5% and asthenia grade III were 3.4% versus 17.5%. The remaining of safety parameters were comparable, although neutropenia grade III favored the LipoGem arm.
Conclusions: Lipoplatin appears more effective in advanced NSCLC when combined with gemcitabine, especially against adenocarcinomas, than cisplatin-gemcitabine, which appears to be more effective against squamous cell carcinomas. Lipoplatin has a more favorable safety profile than cisplatin, particularly regarding nephrotoxicity, neurotoxicity and asthenia.

9089 POSTER

Optimal duration of 1st- and 2nd-line chemotherapy (CT) for advanced non-small cell lung cancer (NSCLC)

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Background: Six vs 3−4 cycles of 1st-line CT do not offer an overall survival (OS) benefit to patients (pts) with advanced NSCLC and are associated with increased toxicity and potential for worse quality of life. No randomized, prospective data exist on the optimal duration of 2nd-line CT. This retrospective study aimed to: i) confirm the lack of impact of 1st-line treatment duration on efficacy outcomes; ii) evaluate the impact of treatment duration in the 2nd-line setting.

Methods: Eligible pts had received a minimum of 4 cycles of 1st- (n = 95) or 2nd-line (n = 55) CT for stage IIIB/IV NSCLC in clinical trials of the ATOM group, Udine, Italy, or the National Cancer Institute, Genoa, Italy. Trials included one in the elderly, and the addition of biological agents to CT. The achievement of at least stable disease was required. RECIST criteria were used for response assessment. The proportion of pts achieving a complete or partial response, as well as its timing and any subsequent tumor shrinkage, were analyzed by treatment line. Median progression-free survival (PFS) and OS were calculated as well.
Results: Forty-eight of 95 chemona?ve pts responded, after respectively 2 (61%), 4 (31%) and 6 cycles (8%). Sixteen (55%) and 9 (41%) pts who had responded by the 2nd and 4th cycle - and continued on treatment - showed median further tumor shrinkage of 16% (range 1−52%) and 6% (range 1−11%), respectively. In pts responding after 2 vs 4 cycles, median PFS was of 7.1 vs 7.5 months; corresponding OS figures were 15.4 vs 10.9 months. In the 2nd-line setting, 3 (25%), 7 (58%) and 2 (17%) pts responded after respectively 2, 4 and 6 cycles. One and 2 pts who had responded by the 2nd and 4th cycle showed a subsequent tumor shrinkage of 25%, 5% and 24%, respectively.
Conclusions: Approximately 90% of objective responses occurred in chemona?ve pts by the 4th cycle; only minor tumor reduction was achieved with further CT, at the likely expense of increased toxicity. Earlier response was associated with seemingly longer median OS. In the 2nd-line setting the achievement of response appeared slower. These results support the discontinuation of 1st CT after 4 cycles and suggest the same is true for 2nd line CT.

9090 POSTER

A phase I/II study of oxaliplatin and docetaxel in the treatment of relapsed non-small cell lung cancer

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Background: Docetaxel, pemetrexed and the epidermal growth factor tyrosine kinase inhibitors are established as standards of care in the second line treatment of patients with advanced non-small cell lung cancer (NSCLC). Oxaliplatin has been demonstrated to have activity in this setting. We aimed to establish the maximum tolerated dose of oxaliplatin in combination with docetaxel in the treatment of relapsed NSCLC and establish preliminary evidence of efficacy for the combination in this setting.
Materials and Methods: A phase I/II dose escalating study was performed (table). A decision on tolerability and subsequent dose level expansion or escalation was based on: 1) the observed toxicities with 2 episodes of febrile neutropenia occurring in 2 of 6 or less patients being a dose limiting toxicity, and 2) dose delays.

Dose level	Oxaliplatin dose (mg/m^2)	Docetaxel dose (mg/m^2)	Treatment days	Schedule (days)
1	85	40	1, 15	28
2	85	50	1, 15	28
3	85	60	1, 15	28
4	100	50	1	21
5	130	50	1	21
6	130	60	1	21

Results: Dose level 3 was discontinued after recruitment of 3 patients due to febrile neutropenia. Dose level 2 resulted in significant dose delays due to neutropenia. One patient died from pneumonitis on this level and another had grade 3 erythema multiforme. Therefore a 3-weekly dose escalation schedule was employed through levels 4 to 6. At level 6, 9 patients developed grade 3 or 4 neutropenia and growth factor support was required. One patient died due to aspergillus pneumonia. The schedule was otherwise well tolerated. In all, 20 patients were recruited to these 3 cohorts with 4 at level 4, 6 at level 5 and 10 at level 6. Partial responses were recorded in 4 of the 20 evaluable patients (20%) with a median time to tumour progression of 4.2 months (95% CI 1.4, 7.0) and median overall survival of 8 months (95% CI 4.1, 14.7). 19 of these 20 patients have progressed at the time of analysis.
Conclusion: Oxaliplatin may be combined with docetaxel and is relatively well tolerated. The dose limiting toxicity is neutropenia with growth factor support required at level 6. A 20% response rate on the 3-weekly schedule compares favourably with the previously used agents and suggests that the combination may be worth pursuing in relapsed disease.

9091 POSTER

Activity, safety and compliance of sequential chemotherapy with cisplatin (CDDP) plus oral vinorelbine (VNRos) followed by three-weekly docetaxel (DOC) as first-line treatment for advanced non-small cell lung cancer (NSCLC): a single-centre phase II study

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Background: Sequential administration of CDDP-based doublet chemotherapy followed by a taxane is a possible strategy to reduce the risk of drug resistance thus improving treatment outcome in advanced NSCLC, while avoiding the potentially increased toxicity expected with concurrent administration.
Patients and Methods: Thirty-two consecutive chemo-naïve patients (pts) with measurable stage IIIB/IV NSCLC were enrolled: M/F 20/12; median age 54 years (range 39−65); ECOG PS 0/1: 24/8; 19 adenocarcinoma, 10 squamous cell carcinoma, 3 large cell carcinoma; ⩾3 metastatic sites in 5 pts. Treatment consisted of CDDP 80 mg/m^2 i.v. on day 1 plus VNR 60 mg/m^2 *os* days 1−8, every 3 weeks, for 3 cycles, followed by 3 cycles of DOC 100 mg/m^2 i.v. on day 1 every 21 days, regardless of the response. Palonosetron-based antiemetic prophylaxis was provided.
Results: All pts competed the planned 6 cycles of chemotherapy. The overall response rate (RR) after the CDDP/VNR phase was 31% (95% CI:22−54)with CR 6%, 47% of pts had stable disease and 12% progressed. During the DOC phase 2 pts who had had a PR achieved a CR, while 6 pts with SD obtained a PR; no further PD was observed. The ORR to the entire sequential treatment was 56% (95% CI: 39−71). Median response duration was 8 months, median PFS was 10 months (range 4−23+); 26 pts received 2nd line chemotherapy, alone or with palliative radiotherapy (12 pts). Both phases of the protocol were well tolerated, and the oral formulation of VNR allowed good patient compliance. WHO grade 3 neutropenia occurred in 18.7% in the CDDP/VNR phase and 15.6% in the DOC phase; G-CSF support was given in 6% of cycles; only 2 pts experienced febrile neutropenia. Non-haematological toxicities were moderate, with grade 1−2 peripheral neurotoxicity in 15% of pts, grade 1−2 asthenia in 18% of pts and gr.1 diarrhoea in 5% during the DOC phase; nausea/vomiting did not exceed gr.1.
Conclusions: Our results confirm the activity and feasibility of such a sequential approach in advanced NSCLC pts with good PS as up-front treatment, allowing the administration of full dose single agent without significant increased toxicity.

9092 POSTER

Study on concomitant radiotherapy and chemotherapy combined with endostatin for IIIb and IV stage non-small cell lung cancer

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Purpose: To evaluate the short-term efficacy and toxicity of concomitant radiotherapy and chemotherapy combined with endostatin for IIIB and IV stage NSCLC.
Patients and Methods: 25 cases with IIIB and IV stage NSCLC were treated with 4 cycles of paclitaxel (135 mg/m^2, d1), cisplatin (25 mg/m^2/d, d1−3) and endostatin(15 mg/d, d1−14). By concomitant radiotherapy (Intensity Modulated Radiation Therapy, IMRT), the total dose of central tumor and lymph node are the same: 66−70 Gy, peripheral tumor is 70−90 Gy.
Results: All patients finished treatment. Leucopenia (16/25) was 64%. Two patients developed grade 3 acute radiation-induced esophagitis(8%), and 1 developed grade 3 radiation-induced pneumonia (4%). The overall response rate was 73.8%. The 1-year overall survival rate was 76%. The 1-year local progression-free survival rate was 52%. Local recurrence rate was 27.6%, distant metastasis rate was 48%. Distant metastasis was the major reason for deaths.
Conclusions: concomitant radiotherapy and chemotherapy combined with endostatin for IIIB and IV stage NSCLC can be well tolerated and the toxicity is tolerable. Results of this study are encouraging, though long-term results should be followed up.