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A Phase I/II Study of Amrubicin and Irinotecan in Patients With Extensive Disease Small Cell Lung Cancer WJTOG0302

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Background: After an apparently successful frontline therapy to extensive disease small cell lung cancer (ED-SCLC), most patients (pts) experience recurrence. New drugs combinations are urgently needed to control SCLC more effectively. Amrubicin hydrochloride (AMR) is a synthetic anthracycline anticancer agent and a potent topoisomerase II inhibitor. Preclinical studies have shown that the use of a combination of topoisomerase I and II inhibitors completely arrests catalyze the relaxation of supercoiled chromosomal DNA, which results in synergistic cytotoxicity.
Methods: The phase I/II studies were designed to determine the maximum tolerated dose (MTD), the recommended dose (RD) and the efficacy of AMR in combination with a topoisomerase I inhibitor, irinotecan (CPT) for pts with newly diagnosed ED-SCLC with ECOG performance status (PS) 0−1 using a standard 3+3 dose escalation design. Pts were treated at 3-weekly intervals with a dose-escalated AMR (days 1−3) plus CPT (days 1 and 8) with granulocyte colony stimulating factor (G-CSF) support (days 4−7, 9−15).
Results: From Mar 2004 to Dec 2008, a total of 23 pts was enrolled with 1 screen failure. The median age was 65 years (50 to 70) and 17 were male. Median number of chemotherapy cycles was 4 (1 to 7). In a phase I study, 11 pts were treated. No DLTs were observed in the first 3 pts in the level 1 dose of 35 mg/m^2 AMR and 50 mg/m^2 CPT. However, 2 pts have shown DLTs in the level 2 dose of 40 mg/m^2 AMR and 50 mg/m^2 CPT. One had grade (G) 3 febrile neutropenia (FN), and the other had G4 neutropenia on 4 consecutive days, G3 FN and G3 diarrhea, ended up as toxicity related death. Data and Safety Monitoring Committee recommended additional 6 pts exploration in level 1. In these 6 pts, 3 pts showed DLTs (2 pts: G3 FN, and 1 pt: G4 neutropenia). The MTD was determined as the dose of level 2, and the RD was the dose of level 1. Phase II study was performed with a dose of the RD. A total of 21 pts (9 pts: phase I, 12 pts: phase II) were evaluated for safety. G3/4 hematological toxicities included neutropenia 38.1/33.3%, leukopenia 14.3/19%, anemia 19/4.7%, and thrombocytopenia 9.5/4.7%. G3 or 4 non-hematological toxicities included nausea/vomiting 23.8%, FN 19%, diarrhea 9.5%, and decrease of PS 9.5%. Other common adverse events were constipation, dyspnea, hyponatremia, hypocalcemia, skin disorders and stomatitis. A total of 20 pts (0 CR, 14 PRs, 3 SDs, and 3 NEs) were evaluated for efficacy. An overall response rate was 70% (95% CI: 46−88). Progression free survival was 6.5 months (95% CI: 5.1−9.3), and 1 year survival rate was 73% (95% CI: 47−88).
Conclusions: The combination of AMR and CPT with G-CSF support against ED-SCLC appears to have severe non-hematological adverse events despite a highly antitumour activity. These results suggested this combination is not recommended for practice use. Patient selection such as UGT1A1 is warranted for further evaluation of this combination of topoisomerase I and II inhibitors.

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Efficacy and Safety of Pemetrexed-Cisplatin for Advanced Non-Squamous Non-Small Cell Lung Cancer − a Galician Lung Cancer Group Study

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Background: Recently a noninferiority study was the first prospective phase III study in NSCLC to show survival differences based on histologic type. It proved that in adenocarcinoma and large-cell carcinoma histology advanced NSCLC, cisplatin/pemetrexed provides better efficacy than cisplatin/gemcitabine. We conducted a multicenter study in advanced NSCLC to evaluate the tolerance and efficacy of first-line pemetrexed-cisplatin in non-epidermoid carcinoma.
Materials and Methods: Patients received pemetrexed (500 mg/m^2 day 1) and cisplatin (75 mg/m^2 day 1) every 21 days (PC) with restaging after 3 and 6 cycles. The primary end point was to evaluate the overall response rate and the secondary were the median overall survival and the progression-free survival.
Results: Ninety-four patients were enrolled from seven centers across Galicia. Overall response rate was 42.9% (1.4% of complete response and 41.4% of partial response). Median overall survival was 12.6 months (95% confidence interval, 6.76 to 18.43); progression-free survival was 4.17 months (95% conficence interval, 3.3 to 5). The treatment was well tolerated, with the most common treatment-related side effects being grade 1 and 2 asthenia (58.55%), anemia (44.94%) and nausea (30.34%). Grade 3 and/or 4 toxic reactions were neutropenia (7.86%, 4.49% with fever), vomiting (5.62%), anemia, nausea and asthenia (2.25%).
Conclusion: This regimen was associated with acceptable toxicity and relatively long survival in patients with advanced adenocarcinoma and large-cell carcinoma lung cancer.

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The Feasibility of Platinum-based Combination Chemotherapy for Advanced Lung Cancer With Idiopathic Interstitial Pneumonias

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Background: Idiopathic interstitial pneumonias (IIPs) appear to be associated with lung carcinogenesis. In particular, the incidence of lung cancer in patients with idiopathic pulmonary fibrosis (IPF) is higher than that in the general population. Therefore, IIPs are one of the most common complications in patients with lung cancer. In lung cancer with IIPs, the most serious expression of toxicity in Japan is acute exacerbation (AE) of IIPs caused by anticancer treatment. Nevertheless, there is neither evidence nor no consensus around the issue as to whether aggressive treatments such as chemotherapy are appropriate for non-curative lung cancer with IIPs. We therefore conducted a prospective study of combined chemotherapy to assess acceptability, in terms of safety and potential efficacy, in treatment of advanced lung cancer with IIPs.
Patients and Methods: Pathologically confirmed, chemotherapy-naïve patients with advance lung cancer with IIPs who were ineligible for curative radiotherapy were enrolled. Patients with small cell lung cancer (SCLC) received etoposide at a dose of 100 mg/m^2 on Days 1 to 3, and carboplatin every 28 days at a target dose of area under the curve (AUC) 6.0 on Day 1 (CE). And patients with non-small cell lung cancer (NSCLC) received paclitaxel at a dose of 100 mg/m^{2}on Days 1, 8, 15, and carboplatin every 28 days at a target dose of area under the curve (AUC) 5.0 on Day 1 (CP).
Results: Between July 2002 and October 2008, a total of 35 Japanese patients (28 males and 7 females) were enrolled. The median age of patients was 70 years (range: 33−81). Historogically, SCLC and NSCLC were observed in 17 and 18 patients, respectively. 14 patients were clinically or histologically confirmed IPF. The overall response rate was 88% in Group CE and 61% in Group CP. The progression-free survival and the median survival time were 5.5 months and 8.7 months in Group CE and 5.3 months and 10.6 months in Group CP, respectively. Two patients (5.7%) had Grade 5 acute lung injury (AE of IIPs). Throughout the follow-up period, AE developed in 10 of 35 patients from this study. We conducted univariate analysis for clinical factors and examination data before initial chemotherapy. However, there was no statistically significant risk factor for AE even under variety of conditions.
Conclusions: The combination chemotherapies of carboplatin plus etoposide or paclitaxel used in the present study was effective and safe for advanced lung cancer patients with IIP. This is the first report indicating that patients with advance lung cancer with IIPs may benefit from chemotherapy. The results from this study would support, on ethical grounds, the conduct of a large-scale study to evaluate thiese regimens.