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Assessment of pulmonary reaction after carbon ion irradiation in the patients with stage I non-small cell lung cancer

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Experiences about phase I/II clinical trial of carbon ion irradiation against stage I non-small cell lung cancer (NSCLC) was prospectively evaluated with especial respect to pulmonary reaction found on computed tomography (CT) in terms of treatment dose, volume and dose-volume histogram (DVH). 46 patients (35 male, 11 female) aged ranging from 49 to 82, with medically inoperable stage I NSCLC received carbon ion radiation from 1994 to 1998. The follow-up duration was 6 to 54 months (median:23). Since one patient had two different primaries, 47 NSCLCs were evaluated. 27 tumors were smaller than 3cm, while 20 tumors were ranging from 3 to 7cm. In the phase I/II study, the dose escalation in 18 fractions in 6 weeks was performed from 59.4 photon gray-equivalent dose (GyE) to 95.4GyE by the step of 10% increase. Clinical target volume (CTV) was determined to cover gross tumor volume with more larger than 5mm margin (median; 46.8ml). Prophylactic irradiation to the hilus and mediastinum was not applied. Chest CT was serially performed before and 1, 3, 6, 9, 12 and every 6 months after the end of treatment. CT findings classified into two discrete categories: "Pleural " (pleural thickening and/or effusion) and "Pulmonary" reaction. The pulmonary reactions were classified according to the modified scoring system proposed by Bush et al.(grade0: no remarkable change, grade1: slight increase in density with no consolidation, grade2: consolidation involves less than 50% of the irradiated portion, grade3: consolidation involves more than 50% of the irradiated portion, grade4: changes spreading beyond the boundaries of radiation field) (AJR, 1999:172;753-9). DVH was calculated for every patient and the volume irradiated more than 20GyE (V20) and 40GyE (V40) was used for analysis. Overall and cause-specific 5-year survivals were 48% and 66%, respectively (median follow up: 43 months) (Kaplan-Meier). Pleural reaction was observed in 23 patients (49%) at 1 to 12 months after the initiation of the treatment (median: 4 months). Such pleural reaction was observed in the patients with large CTV (rs=0.552, p=0.00018). Pulmonary reaction was observed in 45 (98%) patients (grade0: 2, grade1: 14, grade2: 19, grade3: 12, grade4: 0). No correlation was found between the grade of pulmonary reaction and CTVs or irradiated doses, but the grade of pulmonary reaction showed a statistically significant correlation with V20 (rs=0.4, p=0.007) and V40 (rs= 0.43, p=0.0037).

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Impact of neoadjuvant chemotherapy on RT treatment planning for stage III NSCLC patients

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Purpose: Patients with inoperable NSCLC who respond to neoadjuvant chemotherapy have a reduction in the tumor size as compared to the pre-chemotherapy volume, changing the targeting of the subsequent RT treatment plan. This may lead to a decrease in the amount of irradiated normal lung and surrounding normal tissues and a corresponding decrease in the risk of developing normal tissue toxicity. The aim of this study was to compare RT plans designed to target the pre- and post-chemotherapy tumor volumes and evaluate the clinical benefit with dose-volume parameters.

Methods: Ten patients with Stage III NSCLC underwent CT scan of the chest prior to and after the administration of a two month course of neoadjuvant chemotherapy consisting of cisplatin and Navelbine. These patients received an average of 73Gy (60-84) on a dose escalation trial. The gross tumor volume (GTV) (including the involved lymph nodes) decreased in size after chemotherapy in all patients an average (range)of 77cc (11-210). For each patient, the original treatment plan for the post-chemotherapy planning target volume(PTV) was compared to a plan with identical beam arrangement but with altered field shapes for the pre-chemotherapy PTV. Treatment planning goals included minimum target volume dose of 95% of the prescription dose, minimizing the amount of normal lung irradiated, limiting cord dose to <50Gy, esophagus volume (Veff) to 33% < 80Gy, and heart Veff to 100% and 33% < 40 and 65Gy respectively. For each patient, the changes in the lung dose-volume parameters such as mean lung dose, lung volume receiving >20 Gy (V20) and normal tissue complication probability (NTCP) were compared. NTCP was calculated with the Lyman, Kutcher, Burman method with Kwa's parameter fit (Kwa IJROBP 42, 1998)

Results: Targeting the post-chemotherapy PTV resulted in the following average decreases (range): mean lung dose by 4Gy (0-10), NTCP by 8% (0.3-17), V20 by 6% (0.2-13), maximum cord dose by 4Gy (0-15), esophagus Veff by 13% (0-74), whole heart Veff by 22% (0-65) and partial heart Veff by 5.5% (0-16).

Conclusion: Radiation treatment plans for patients who respond to neoadjuvant chemotherapy result in a clinically significant lower probability (8% on average) of developing radiation pneumonitis. Radiation doses to other surrounding normal tissues can also be decreased, specifically the spinal cord, esophagus and heart, thereby decreasing the risk of late complications involving these structures.

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A phase I study of irinotecan and carboplatin with concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer

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Purpose: A phase I clinical trial was performed to evaluate the efficacy and toxicity of weekly irinotecan with daily carboplatin and concurrent thoracic radiotherapy in patients with locally advanced non-small-cell lung cancer (NSCLC).

Patients and Methods: Thirty-one previously untreated patients with unresectable stage III NSCLC were enrolled in a phase I study. Patients received weekly irinotecan plus carboplatin (20 mg/m2 daily for 5 days a week) for 4 weeks and thoracic radiotherapy (60 Gy in 30 fractions). The irinotecan dose was escalated from 30 mg/m2 in increments of 10 mg/m2.

Results: Four irinotecan dose levels were given and 30 patients were assessable. Their median age was 62 years (range: 52-72 years), 28 had a performance status of 0-1 and 2 had a performance status of 2, and 12 had stage IIIA disease and 18 had IIIB disease. There were 19 squamous cell carcinomas, 10 adenocarcinomas, and 1 large cell carcinoma. The dose-limiting toxicities were pneumonitis and thrombocytopenia. The maximum tolerated dose of irinotecan was 60 mg/m2, with 3 patients developing grade 4 pulmonary toxicity (1 died of pneumonitis). Three patients achieved complete remission and 15 had partial remission, for an objective response rate of 60.0%. The median survival time was 14.9 months, and the 1- and 2-year survival rates were 51.6% and 34.2%, respectively.

Conclusion: The major toxicity of this regimen was pneumonitis. This therapy may be active against unresectable NSCLC and a phase II study is warranted.

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Phase II study of low-dose weekly paclitaxel as second-line treatment for advanced non-small cell lung cancer

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Purpose: To investigate the activity and toxicity of low-dose weekly paclitaxel (WP) as single-agent in patients with advanced non-small cell lung cancer (NSCLC) who experienced recurrence or failure to previous chemotherapy regimen.

Patients and methods: From August-98 to August-00, twenty-nine patients with metastatic or unresectable NSCLC were treated with 80 mg/m2 WP as 1-hour infusion, without rest period, until disease progression, unacceptable drug toxicity or after achievement of best response. The median age was 66 (range 42 to 81); 19 patients had ECOG-PS 1 and 10 PS 2. The predominant histology was squamous (21 patients); twenty-one patients had stage IV disease, 7 patients had stage IIIB and 1 had stage IIIA. Sixteen of the 29 patients had initially responded to platinum-based therapy, 6 patients had achieved stable disease (SD) and 7 had disease progression (DP) prior to the present chemotherapy regimen. The median time between the last dose of the previous chemotherapy and the start of the weekly paclitaxel was 25 weeks (range = 2 to 106 weeks).

Results: Two (6.9%) patients achieved a complete response (CR) and 8 (27.6%) partial response (PR) for an overall response rate of 34.5% (10 of 29 patients). There were also 12 (41.4%) cases of SD and 5 (17.2%) of DP. Median survival (intent to treat) was 51 weeks (95% CI: 29-73). Treatment was well tolerated. There were no episodes of grade 4

hematological or non-hematological toxicities. Only 1 patient had grade 3 thrombopenia; grade 3 anemia or neutropenia were not observed. Severe non hematological toxicity also was uncommon: grade 1-2 fatigue/asthenia in 27 patients (61%); grade 1-2 motor neuropathy in 26 (59%) and grade III in 4 (9%); grade 1-2 sensory neuropathy in 25 patients (57%); alopecia was mild.

Conclusion: Low-dose weekly paclitaxel regimen has good clinical efficacy with low toxicity in previously treated patients with advanced NSCLC, and may provide an additional treatment option for these population.

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A phase I/II study of weekly irinotecan combined with weekly cisplatin in patients with advanced non-small cell lung cancer

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Purpose: Synergistic effects between irinotecan and cisplatin have been reported. We had conducted a phase I trial combining these agents to determine the maximum-tolerated dose of weekly irinotecan plus weekly 20 mg/m2 cisplatin. Following a phase I study, we have conducted a phase II study to confirm the efficacy and safety of this combination therapy. Methods: For a phase I study, patients with advanced solid tumor, aged ≤ 75 years, performance status ≤ 2, and adequate organ functions were enrolled. They were treated at 4-week intervals using each dose of irinotecan plus fixed dose (20 mg/m2) of cisplatin on days 1, 8, and 15. The starting dose of irinotecan was 40 mg/m2 (level 1), and escalated in 10 mg/m2 increments until the maximum dose of 90 mg/m2 (level 6). In addition to severe toxicities, inability to complete the full-dose chemotherapy was considered as a dose limiting toxicity. After determining the recommended dose, a phase II study was conducted to previously untreated patients with non-small cell lung cancer (NSCLC). Results: In level 6 of a phase I study, dose limiting toxicities were observed in 3 of 9 patients (two for severe toxicities and one for inability to complete the initial two courses). Although the dose of irinotecan did not reach to the maximum-tolerated dose, the dose of irinotecan for the following phase II study was determined 90 mg/m2 according to the study design. For a phase II study, final goal is 100 patients. So far, 32 patients with advanced NSCLC were evaluated. All were assessable for toxicity and response. Response rates of NSCLC was 46% (13/32). Median response durations of NSCLC was 80 days. Total number of cycles administered was 95, and median number of cycles of NSCLC was 3. In 68 of 95 cycles (71.6%), anti-cancer agents were administered without skip. Dose reduction was performed in 25 cycles of 95 cycles. Toxicities were generally mild and reversible; toxicities over grade 3 were as follows; neutropenia (34.4%, 11/32), anemia (21.9%, 7/32), thrombocytopenia (3.1%, 1/32), diarrhea (25%, 8/32), anorexia (28.1%, 9/32), nausea and vomiting (18.8%, 6/32), abdominal pain (3.1%, 1/32). Conclusion: The recommended dose of irinotecan is 90 mg/m2 in the present study. The combination of weekly irinotecan and weekly cisplatin seems to be active against lung cancer

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The sequential administration of cisplatin-etoposide followed by topotecan in patients with extensive stage small cell lung cancer (SCLC). A multicenter phase II study

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We studied the sequential administration of topotecan after cisplatin-etoposide in patients with extensive stage SCLC.

Patients and Treatment: 38 patients with previously untreated extensive stage SCLC received 4 cycles of cisplatin 75 mg/m^2 IV on day 1 and etoposide 100 mg/m^2 IV on days 1–3 every 21 days followed by 4 cycles of topotecan 1.5 mg/m^2 IV on days 1–5 every 21 days. The median age was 63 and the performance status (WHO) was 0, 1 and 2 in 5, 25 and 8 patients, respectively.

Results: All patients were evaluable for toxicity and 32 for response. Overall 5 (16%) patients achieved CR and 15 (47%) PR for an overall response rate of 63% (95% c.i. 45.7–79.2). Among 19 patients achieving PR with cisplatin-etoposide, 4 (21%) achieved CR with topotecan. After a median follow up of 8 months, the median duration of response was 5 months, the time to tumor progression was 6.5 months and the probability of one-year survival was 37%. A total of 136 cycles of cisplatin-etoposide and 89 cycles of topotecan have been administered with a median number of cycles per patient 4 for each regimen. There were 2 toxic deaths after cisplatin-etoposide associated with grade IV febrile neutropenia. Treatment delays due to toxicity occurred in 17 cycles of cisplatin-etoposide and 20 cycles of topotecan while doses were reduced in 7 and 4 cycles, respectively. The incidence of grade 3–4 neutropenia, thrombocytopenia and febrile neutropenia was 24.5%, 2% and 3% after cisplatin-etoposide and 21%, 11% and 1% after topotecan. Non-hematologic toxicity was mild. The delivered dose intensity was 100% for cisplatin and etoposide and 82.5% for topotecan.

Conclusions: The sequential administration of cisplatin-etoposide followed by topotecan is a feasible and effective regimen in extensive stage SCLC.

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Chemotherapy with gemcitabine in elderly patients (or in patients not candidate for a cisplatin regimen) with advanced NSCLC: a multicenter phase II study

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Rationale: In a previous study we demonstrated in elderly patients with advanced NSCLC and in pts not candidate for a cisplatin regimen due to concomitant diseases or poor performance status that Gemcitabine administered at the dose of 1000 mg/sqm iv days. 1,8,15 every 28 is active and well tolerated (S.Ricci, Lung Cancer 2000). To improve the dose intensity of Gemcitabine and the compliance to the treatment we have performed a multicenter phase II study with the following schedule: Gemcitabine 1500 mg/sqm iv days 1,8 every 21 for 4 courses. The pts. with SD or OR after 4 courses of chemotherapy were randomized to receive futher 4 cycles of manteinance chemotherapy with Gemcitabine 1200 mg/mq iv days. 1,8 every 21 or best supportive care in order to evaluate the impact on TTP and OS. Patients characteristics: 110 patients were enrolled, 98 males and 12 females; median age 75 yrs range (50-84). PS: 0 = 42, 1 = 44, 2 = 22, 3 = 2; 30 pts. were adenocarcinoma., 53 squamous, 27 NSCLC.

Total number of cycles administered was 270 (median 4 cycles); we observed the following hematological and not hematological toxicity

	G1	G2	G3	G4
Neutropenia	0,7	2,6	0,7	–
Nausea/Vomiting	18,9	7,8	–	–
Thrombocytopenia	3,0	–	0,4	–
Diarrhoea	2,2	0,4	–	–
Anemia	15,6	3,0	0,7	–
Stomatitis	1,1	2,2	–	–
Skin Toxicity	1,1	–	–	–
Fever	8,9	2,2	–	–

Responses: up to now 88 patients are evaluable for response: 12 (13,6%) PR, 23 (26,1%) SID, 53 (60,2%) PD.

Conclusions: The Gemcitabine administered at the dose of 1500 mg/sqm iv days. 1,8 every 21 is active and well tolerated with a good compliance in elderly pts or in pts not candidate for a cisplatin regimen. The study is ongoing in order to evaluate the role of maintenance therapy.

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ZD0473 phase II monotherapy trial in second-line non-small cell lung cancer

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Aims: ZD0473 (cis-amminedichloro[2-methylpyridine]platinum [II]) is a new generation platinum drug designed to have an extended spectrum of antitumor activity and overcome platinum resistance mechanisms. A Phase II open-label, multicenter trial, was designed to assess the efficacy and tolerability of ZD0473 in patients with non-small cell lung cancer (NSCLC) who have failed previous platinum-based therapy.