P1-233 SCLC: Cytotoxic Chemotherapy Posters, Mon, Sept 3

Efficacy of carboplatin (C) and etoposide (E) for extensive stage small cell lung cancer (ED-SCLC)

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Background: Standard chemotherapy for SCLC is considered to be a cisplatin based combination. C has broad spectrum anti-tumor activity and is commonly used as a less toxic alternative to cisplatin. The purpose of this study is to investigate the activity and toxicity of C and E in patients (pts) with previously untreated ED- SCLC.

Methods: Patients characteristics included pathologically diagnosed extensive SCLC, measurable or evaluable disease, ECOG performance status (PS) 0-3, and adequate organ function. Chemotherapy consisted of (C) AUC 6 IV day 1, (E) 100 mg/m^{2}IV day 1-3. This schedule was repeated every 21 days for maximum 6 cycles. Data were collected prospectively. Survival data was calculated from date of treatment to date of death or last known follow up. Kaplan-Meier curves and Log Rank test were used for studying survival rates.

Results: From 01/01 to 11/06, 56 Chemotherapy and radiotherapy naive pts were enrolled and 52 were evaluable. Patients characteristics were as follows: median age 62 years (range 39-76); 50 male and 2 female; ECOG PS 0-1 in 43 pts, PS 2-3 in 9 pts. 14 pts had multi-organ metastasis. 33 patients died. Seven patients lost to follow up. A total of 243 cycles were administered: median 4.68 (range 1-6). Dose reductions took place in 2.8% of cycles. The overall response rate was 71% (25% CR, 46% PR). Median overall survival was 337 days (95% [CI 272-401]), one-year and two years survival were 44.8% and 13.3%, respectively. Log Rank test demonstrated that multi-organ metastasis lead to a trend to the poor survival (P=0.055). Grade III-IV neutropenia, leukopenia, thrombocytopenia, anemia were detected in 16%, 6%, 4.5%, 3.7% of courses, respectively. Febrile neutropenia was developed in 5 patients. There was no toxic death. Non-hematological toxicity was generally mild.

Conclusions: On the basis of these results, It seems that C+E is active and tolerable in ED-SCLC patients and our outcomes are in line with other published platinum-based studies.

SCLC: Molecular Targeted Therapy

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N-cadherin, a potential novel therapeutic target in small cell lung cancer

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Background: New treatment ideas are needed in small cell lung cancer (SCLC). N-cadherin which is associated with increased tumor invasiveness is a potential novel therapeutic target. It seems reasonable to test recently developed cyclic peptide N-cadherin antagonists in tumors with high N-cadherin expression, and it seemed likely that high N-cadherin expression would occur more frequently in aggressive tumors like SCLC. Our objective was to determine the frequency and biological significance of N-cadherin expression in SCLC.

Methods: We retrospectively analyzed 86 patients with small cell lung cancer, most of whom received treatment: chemotherapy with or without radiation. We reviewed their clinical charts and obtained: date of diagnosis, age, gender, performance status, treatment dates and treatment response (CR/PR, stable disease, progression), and death or last encounter date. We also analyzed their pathology specimens for frequency of expression of N-cadherin and grouped them into three categories: no expression, some expression of N-cadherin >1% but <35%, and strong expression 36-100%. Subsequently, we determined the correlation between the N-cadherin frequency groups and the overall survival for all 86 patients. We also determined the time to progression in a subset of 56 patients (with available treatment response data).

Results: Out of the 86 patients, 18 (21%) did not express N-cadherin, 10 (11.6%) patients showed >1% but <35% expression of N-cadherin, and 58 (67.4%) had a strong expression >36%-100%. There was no association found between N-cadherin expression and overall survival using either the Log-Rank Test or the Wilcoxon Test. In the subset of 56 patients with available treatment response data there was no association between N-cadherin expression and progression free survival.

Conclusions: N-cadherin was expressed relatively frequently in this group of SCLC patients, and these results suggest that phase II trials of the novel cyclic peptide N-cadherin antagonists are warranted in SCLC. N-cadherin did not appear to have prognostic value in our study.

SCLC: Radiation

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Once a day (QD) thoracic 3D conformal radiotherapy (XRT) for patients with limited stage small-cell lung cancer (SCLC) treated concurrently with etoposide and cisplatin (EP): results of a single institution retrospective experience.

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Background: Standard treatment of limited-stage SCLC is based on EP chemotherapy (CT) given concurrently with early twice a day (BID) thoracic XRT (45 Gy in 30 fractions) and prophylactic cranial irradiation (PCI) in case of complete response (CR). BID thoracic XRT is difficult in common practice and often causes severe esophagitis. Option of a more convenient QD schedule with a higher dose conformal 3D XRT needs to be studied.

Patients and Methods: Patients (pts) with limited-stage SCLC received P (100 mg/m^2 d1) - E (100 mg/m^2 d1-3) for 4 courses administered every 3 weeks with a 20% dose reduction during XRT (cycle 2 and 3). QD 3D conformal thoracic XRT began concurrently with the second course and delivered 60 Gy (30 fractions of 2 Gy) in 6 weeks. PCI (24 Gy, 12 fractions) was given for complete responders. Results were retrospectively analysed.

Results: From 1996 to 2004, 38 consecutive pts (median age 61 (42-77), PS 0-1: 92%, 2-3: 8%) were treated. 84% pts received 4 CT cycles and 86% pts full thoracic XRT; 26 pts underwent PCI. Objective response rate is 84% with 53% CR. With a median follow-up of 26 months, median disease-free survival, median survival and 5-year survival rate are respectively 10,6 months [7,3-15,3], 17,6 months [11,0-31,7] and 29%. Intrathoracic infield and brain isolated failures occurred in respectively in 30% and 22% pts. Main toxicities were neutropenia (55% grade 4 neutropenia with 4 deaths due to febrile neutropenia concerning PS 2-3 and elderly pts) and esophagitis (29% grade 3+). Grade 2+ radiation pneumonitis occurred in 5% of pts.

Conclusion: High dose QD XRT given concurrently with EP CT is feasible but must be restricted to good PS patients. Esophagitis remains a limiting toxicity. In spite of broad inclusion criteria (no limit of age, PS 2-3), median and 5-year survival rate are similar to those reported by Turrisi et al. NEJM, 340(4)265-271,1999. These results justify the CONVERT phase III study wich will compare QD high dose XRT (66 Gy) to BID thoracic XRT (45 Gy) given concurrently with EP CT in limited-stage SCLC.

Fig. 1: Comparison of efficacity and toxicity with Turisi's studie.

	Croix Rousse	Turrisi	
		QD XRT	BID XRT
Survival			
Median survival	17,4 months	19 months	23 months
5 year-survival	29%	16%	26%
Toxicity			
Grade 3+ neutropenia	68%	75%	80%
Grade 3+ Esophagitis	29%	16%	31%
Gr 3+ radiation pneumonitis	3%	3,20%	6%
Treatment related deaths	11%	2%	3%

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A long-term result by hyperfractionated radiotherapy with concurrent chemotherapy for limited-stage small cell lung cancer (LD-SCLC): a retrospective analysis in a single institution

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Purpose: To determine the long-term treatment results of hyperfractionated thoracic radiotherapy with concurrent chemotherapy for clinically diagnosed LD-SCLC patients.

Materials and Methods: Between 1996 and 2004, 46 patients with histologically confirmed SCLC were diagnosed with limited-stage disease using physical and radiological examinations. Patient characteristics. Gender: M/F=36/10. Median age: 64 years (21-82), Performance status: 0/1/2=13/30/3, T1/2/3/4=8/11/7/20, N0/1/2/3=3/5/25/13, Clinical stage: 2A/2B/3A/3B=1/4/17/24. For chemotherapy, dose-intensive (DI) regimens such as CODE and CAV containing doxorubicin were preferably used as a neoadjuvant setting before 1998, and, combinations of cisplatin or carboplatin with etoposide or CPT-11 (PE/CPT) were used after 1998. Twice-daily thoracic radiotherapy was performed with 6/10 MV- X rays with at least a 6-hour interval and total dose was 45 Gy/1.5 Gy bid in 3 weeks. Radiotherapy was started on day 1 immediately after the 1st/2nd/3rd/4th cycle of chemotherapy (cisplatin: 80 mg/m^2 i.v. on day 0 and etoposide: 100 mg/m^2 p.o.) in 18/13/3/12 pts, respectively. Primary lesions and enlarged lymph nodes with ipsilateral hilum and mediastimum (also with supraclavicular region, when necessary) were covered with AP portals of 30 Gy, then gross tumor volumes were irradiated with oblique portals of 15 Gy. A prophylactic cranial irradiation (PCI) of 24-30 Gy/2.0-2.5 Gy was used in selected cases. Local tumor responses were assessed by RECIST. Survical results were analysed by the Kaplan-Meier method. Treatment-related toxicities were evaluated according to the CTCAE v3.0.

Results: All of the patients could successfully receive 45 Gy of irradiation. Four cycles of scheduled chemotherapy mostly at a 3-week interval were completed in 41 out of 46 patients (89%). This combined treatment resulted in an overall response rate of 98%, including 59% (27/46) complete responses. Loco-regional recurrences were detected on follow-up CT scans in 27% (12/46) of cases, all of which were detected within gross tumor volumes at the time of treatment planning. No clinical/treatment factors were significantly correlated to local recurrence. Distant metastasis were found in 67% (30/46), and the most frequent site of first metastasis was brain (39%), while PCI were done in 33% (15/46). Overall 46% of the patients were diagnosed with brain metastases at some time and subsequently treated by a palliative radiotherapy. For all patients, the median survival time (MST) was 22.7 months and the 2/3/5 year survival rates were 44/32/22%. The group of the patients treated with standard PE/CPT showed better survival than that with DI regimens. ($p<0.05$; Wilcoxon). With standard PE/CPT, MST was 28.6 months and the 2/3/5/ year survival rates were 51/32/24%. Timing of radiation and chemotherapy, use of PCI did not significantly impact on survivals in this study. The major toxicities included grade 3 and 4 acute neutropenia (15% and 64%, respectively), grade 2 and 3 radiation esophagitis (24% and 4%). Radiation pneumonitis were observed as grade 2 and 3 in 7% and 13%, respectively, and one patient died from severe radiation pneumonia and subsequent infectious events.

Conclusions: Hyperfractionated radiation with concurrent chemotherapy was well tolerated and showed favorable responses and survivals in patients with LD-SCLC. Standard PE/CPT showed a superior survival rate to DI regimens. For further improvement of clinical results for LD-SCLC, more effective means of prophylaxis/treatment against brain metastasis should be established.