162

PHOTODYNAMIC THERAPY AND/OR ENDOBRONCHIAL IRRADIATION AS PRETREATMENT IN EXTERNAL RADIATION THERAPY FOR PATIENTS WITH INOPERABLE NON-SMALL CELL LUNG CANCER: AN INTERIM ANALYSIS.

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Photodynamic therapy (PDT) and endobronchial high dose irradiation (HDR) have shown to be effective in the treatment of central intraluminal non-small cell lung cancer (NSCLC). However, the proper place and indication for both modalities is not yet established in relation to external radiation therapy (ERT). A prospective randomized multicenter study was initiated to evaluate the additional effect of PDT or HDR preceding ERT. Patients with histologically proven inoperable locoregional NSCLC, weight loss < 10% and a PS of > 70% were randomized in this three arms study comparing ERT alone with PDT or HDR preceding ERT. PDT, using Photofrin (2 mg/kg, 200 J/cm, 630 nm) or HDR (15 Gy at 1 cm distance along the tumor) is given 2 weeks before ERT (14 x 2.5 + 8 x 2.5 Gy to the tumor area in 4 weeks). Of the 43 patients analyzed so far (♀:♂ = 5:38) 6 presented with stage I and II and 37 presented with stage III. Four patients were ineligible. Of the 39 remaining patients, 12 patients received ERT alone, 12 HDR-ERT and 15 PDT-ERT. The combined treatments were well tolerated when compared to ERT alone. Side effects observed were: moderate radiation fibrosis in 4, minor hemoptysis in 2 patients (PDT-ERT group). Eight patients suffered from grade 2 and 2 grade 3 esophagitis after ERT. Skin photosensitivity was acceptable in the patients treated with PDT. Fatal hemoptysis occurred in one patient 14 months after protocol treatment. A median survival of 16 months was considered as encouraging in this group of mainly stage III patients. Updated results will be presented.

163

PHASE II STUDY OF CISPLATIN (CDDP), IFOSFAMIDE (IFX) AND *VINORELBINE (VNR) IN STAGE IIIB-IV NSCLC.*

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We carried out a phase II study in stage IIIB-IV NSCLC pts to evaluate the toxicity and the activity of the combination CDDP 80 mg/sqm, IFX 3 gr/sqm on day 1 and VNR 25 mg/sqm days 1,8; courses were administered every 3 weeks. WBC count was performed weekly and G-CSF (300 ug s.c. days 11th to 16th) was administered in case of G4 neutropenia lasting more than 48 hours. Patients Characteristics: (all pts had at least one bi-dimensionally measurable target lesion for response evaluation) 49 untreated pts entered the study; median age 61 (range 35-70), PS 0=31, 1= 17; 2=1 stage IIIB:16, IV:33; histology: 27 adenocarcinoma, 19 squamous, 3 large cells. Toxicity: a total of 187 evaluable courses have been administered; median number of courses: 4 (range 1-6). The worst toxicities observed were as follows:

	G 3	G 4
Neutropenia	9,6%	16%
Thrombocytopenia	1,6%	1%
Anemia	5,9%	
Emesis	10,1%	0,5%
Constipation	1,6%	

Alopecia was universal; 19 courses had to be delayed because of neutropenia on day 1; G-CSF was administered in 46 courses (24,5%);only 11 episodes of febrile neutropenia were observed and only 3 pts required hospital admission.
Response to treatment: 35 pts are evaluable for response: 1 CR, 20 PR (60% overall respose rate), 7 stabilization of the disease and 7 progression. The median time to progression is 7 months (range 1-18+ mos); the median overall survival is 12 months (range 1-18+mos).

164

FAVOURABLE SURVIVAL OUTCOME IN PATIENTS WITH SCLC TREATED BY SEQUENTIAL INTENSIVE CHEMOTHERAPY AND HIGH DOSE CHEST IRRADIATION. Chella A, Ribechini A, Lucchi M, *Sainato A, *Silvano G, Mussi A, Angeletti CA.Thoracic Surgery and * Radiotherapy, Univesity of Pisa, Italy.

From October 1988 to Dicember 1991 42 evaluable patients (pts) with SCLC (stage III-IV TNM) underwent sequential treatment by chemoterapy (CT) and radiotherapy (RT). The chemotherapy schedule was: cisplatin (C) 75 mg/m^2 day 1, epirubicin (E) 100mg/m^2 day 1, etoposide (E) 120 mg/m^2 day 1,3,5 every three weeks for six cicles. Complete and partial responders (CR,PR) with limited disease (LD) and CR with extended disease (ED) received thoracic (60 Gy) irradiation. The median age of the pts was 61yrs (35-72). LD occurred in 27 pts while ED in 15 pts. Each patient has been evaluated for toxicity, response, survival and disease free interval (DFI). Mielosuppression and stomatitis were the more frequent side effects. Granulocytopenia occurred in 51% of the 252 courses (grade III-IV WHO). Anemia and thrombocytopenia (grade III-IV WHO) were 7.5 and 20.2% rispectively. Nevertheless a recovery by day 21 was observed in the majority of courses. Severe stomatitis (grade II-III) was experienced in 24.6% of the courses and lasted generally 7-12 days. Acute cardiac toxicity was uncommon. No deaths were related to toxicity. The overall objective response rate to CT was 100%, with 25 pts (59.5%) CR and 17 (40.5%) PR. Seven pts with LD were subsequently converted to CR after RT. Actually nine pts were alive and disease free. The overall actuarial 5-yrs survival was 16.6% (2-yrs survival rate was 59.2% for LD and 26.6% for ED).The median survival for the whole group was 21.5 mths (10-62+), 24 (11-62+) for those with LD and 18 (10-40) for ED. Therty one pts showed local (n=7) or systemic (n=24) relapse with a median DFI of 12.5 mths (4-30) for LD and 10.5 (5-31) for ED. The more frequent site of systemic relapse was the brain (11 pts). In conclusion CEE and sequential high-dose RT induced a high overall response rate with favourable survival outcome despite of their good tolerability.

165

MPV (MITOMYCIN C, CISPLATIN, VINBLASTINE) NEOADJUVANT CHEMOTHERAPY IN THE TREATMENT OF STAGE III NON SMALL CELL LUNG CANCER

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Standard treatment of stage III non small cell lung cancer (NSCLC) is associated to limited long term survival. Neoadjuvant chemotherapy (CT) seems to be related to a significant improvement of surgical resection rate and long term survival. At our Department a multimodality treatment study with MPV neoadjuvant CT, surgery and adjuvant radiotherapy (RT) was started in November 1990 in stage IIIa and IIIb NSCLC patients. To date 38 patients have entered the study (23 stage IIIa and 15 stage IIIb). Mean age was 57 years (39-67). Hystology was epidermoid ca. in 19 cases, adenocarcinoma 11, large cell ca. 3 and unclassified NSCLC in 5. Thirty-four patients have completed the MPV treatment and are evaluable for response and survival. Three complete responses, 24 partial responses, 4 non responders and 3 disease progressions were observed (79.4% major response rate). Two patients died because of tuberculosis reactivation during CT. Chemotherapy was stopped in 5 patients because of nephrotoxicity, in four after response to treatment. No significant mitomycin-related pulmonary toxicity was observed. Surgery was performed in 20 patients. Radical resections could be performed in 16 patients (47% radical resection rate, 68% in stage IIIa and 20% in stage IIIb). A partial resection was also performed. Five pneumonectomies, eleven lobectomies and one sleeve lobectomy were performed. Postoperative period was uneventful in all cases. In particular, no bronchopleural fistulas were observed. Adjuvant RT was performed in 17 patients. Three radically resected cases are still completing the treatment. Out of 31 patients that have completed the combined treatment, 20 are alive after a median follow-up of 24.5 months (6-35). Eleven out of 13 radically resected patients are alive after a median follow-up of 24 months (6-33). MPV chemotherapy is an effective neoadjuvant treatment in stage III NSCLC, with favourable resection rate and encouraging survival. A longer follow-up is however mandatory to evaluate long term survival. Postoperative complications, particularly bronchopleural fistulas, aren't significantly increased by the treatment.

166

MICROVESSEL COUNT (MC) AND TUMOR VESSEL INVASION IN NON SMALL CELL LUNG CANCER (NSCLC): CORRELATION WITH NODAL INVOLVEMENT AND LATE-STAGE DISEASE. Fontanini G., Vignati S., Bigini D., Mussi A.*, Angeletti CA.*, Bevilacqua G. Institute of Pathological Anatomy, Service of Thoracic Surgery*, University of Pisa, Italy.

Neoangiogenesis and vessel invasion represent essential steps for the growth and metastatic spread in human malignancies. The prognostic significance of MC, a measure of tumor angiogenesis, and TVI has been reported in several human cancers and also in early-stage lung tumors. In this study, we evaluated TVI in a group of 361 consecutive patients (324 M and 37 F, mean age 63.2) who underwent surgical resection for lung cancer. In addition, we examined the intratumoral MC in 180 (49.9%) of the same 361 tumors. The vessels were highlighted by the immunocytochemical ABC method using a MAb which recognises FVIII related antigen in formalin-fixed and paraffin-embedded tumors. The microvessels were counted in a X200 field in the most active areas of neovascularization. The tumors were considered as TVI-positive when they harbored tumor emboli in either peritumoral or intratumoral vessels. We compared our findings with various pathological indicators (histotype, N-status, T-status, p-Stage) and with some biological markers (proliferative activity, p53 protein and EGF- receptor). 74 out of 361 (20.5%) cancers harbored tumor emboli in their blood vessels while 287 (79.5%) did not. The presence of tumor emboli within tumor vessels was significantly associated with metastatic nodal involvement (p=0.0003) on the one hand, and with late-stage disease (p=0.002) on the other one. Moreover, node-positive carcinomas demonstrated a significant higher mean MC than did node-negative tumors (32.7vs22.7; p=0.0001). Indeed, MC increased with increasing stage of disease; stage 2-3 tumors showed a higher mean of microvessels (31.8±16.5) than stage 1 tumors (22.1±12.9)(p=0.0001). In addition, MC and TVI are significantly associated (p=0.03). No correlations have been found between these two markers and other parameters such as T-status, histology, proliferative activity, p53 and EGFr expression. These data suggest that: a) TVI and MC represent unfavourable prognostic indicators in NSCLC; b) TVI and MC are important and consequent steps of metastatic spread in human lung tumors. Supported by Italian Association for Cancer Research (AIRC).

167

THE EFFECT OF MEDROXYPROGESTERONE ASETAT TO WEIGHT GAIN AND PERFORMANCE STATUS IN LUNG CANCER

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In this study we aimed to evaluate the effects of medroxyprogesterone acetae (MPA) on primary lung carcinoma patients' body weights, performance status, constitutional symptoms as well as its toxicity. A two armed prospective, non-random model was used. All 70 primary lung cancer patients received different chemotherapy protocols. In Group A(n=40), patients took 1000mg/day PO MPA besides chemotherapy. In Group B (n=30), only chemotherapeutical agents were administered. At the end of 8 weeks therapy. 70% of patients in Group A and 27% of patients in Group B gained a body weight of ≥3kg. This was a statistically significant result (t=3.58, df=68, p<0.01). When performance status was taken into consideration, 52.5% of patients in Group A and 27% of patients in Group B were evaluated to get improved (t=2.08, df=68, p<0.05). An increase of appetite in 52.5%, a decrease of pain in 70% and a better mood in 55% of Group A patients were observed. The toxicity of MPA was acceptable. It was concluded that with these results in lung cancer patients, MPA might be considered to be an effective agent in improving life quality by means of a statistical significant increase in performance status and by preventing anorexia, loss of weight.