groups were equally distributed according to age, sex, histology, ECOG PS and co-morbidity (hypertension, diabetes and VTE). VEGF serum levels were detected by a commercially available ELISA kit (Quantikine Human VEGF Immunoassay R&D systems, Minneapolis, MN, USA) according to the manifacturer's instructions. S100 B serum levels were measured by the enzyme immunoassay Kit NEXUS Dx ™ (SynX Pharma Inc., Toronto, Canada).

Results: Median age was 60.5 years (range 24–79), M/F 57/16, squamous/adeno/large-cell/non specified NSCLC 18/19/11/26, ECOG PS ⩽2: 64 pts (33 pts with BM and 31 pts without BM), ECOG PS 3: 9 pts (5 pts with BM and 4 pts without BM). Three pts had only BM, while the other were plurimetastatic: bone (24 pts (lung (21 pts), liver (11pts) and adrenal glands (16 pts). The mean value (±SD) of serum VEGF was 506 (±432) pg/ml. VEGF levels showed significant association with large cell histotype ($p = 0.041$). Baseline VEGF serum levels were also correlated with ECOG PS ($p = 0.040$) (pts with ECOG PS 0 had lower VEGF levels (417±364 pg/ml) while pts with ECOG PS 3 had higher VEGF levels (944±699 pg/ml). There was also an association between white blood cells and ECOG PS status ($p = 0.040$). An inverse correlation between serum VEGF levels and haemoglobin was found ($r = -0.24$, $p = 0.046$). No difference in VEGF serum levels was found between pts with BM [501 (±443) pg/ml] and without BM [511(±427) pg/ml] ($p = 0.9$). There was a difference between mean VEGF values in the subgroup of pts with only one BM (300±231 pg/ml) vs pts with multiple BM (506±332 pg/ml) even if it doesn't reach a statistical significance ($p = 0.069$). The S100B serum levels for both groups were <0.01 ng/ml.

Conclusions: No significant association was found between S100 beta levels and the patients' clinical parameters. In particular S100B levels does not seem to discriminate pts with and without BM. Elevated baseline serum VEGF levels appear to be related with the degree of metastatic involvement.

1162 POSTER

Weekly Combretastatin A4 Phosphate (CA4P) in combination with radiotherapy (RT): tumour antivascular effects as demonstrated using perfusion computed tomography (p-CT)

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Purpose: The vascular disrupting agent CA4P, when used as a single agent, causes transient reduction in tumour perfusion. CA4P may act synergistically with RT. Tumour vascular changes that occur during treatment with once-weekly CA4P in combination with RT have been measured using p-CT.

Methods/Materials: Following Local Research Ethics Committee approval and written informed consent, patients with histologically confirmed, advanced non small cell lung cancer were enrolled into a Phase IB clinical trial of CA4P combined with external beam RT. They received twice-weekly palliative RT (27 Gy in 6 fractions) over three weeks. Six patients in the first cohort received a single dose of CA4P (50 mg/m^2) after the first 2nd fraction of RT. Six patients in the second cohort received the same dose of CA4P after the 2nd, 4th, and 6th fractions of RT. Quantitative p-CT measurements of whole tumour blood volume and permeability were performed prior to treatment, after RT, before CA4P and at 4 and 72 hours after every CA4P dose.

Results: After the 2nd, 4th and 6th fraction of RT prior to CA4P, tumour blood volume increased by 13% (paired t-test, $p = 0.16$), 34% ($p = 0.06$), and 26% ($p = 0.05$) respectively. Increases in permeability were seen after RT but failed to reach significance. 4 and 72 hours after receiving the 1st dose of CA4P, tumour blood volume decreased by 15% ($p = 0.03$) and 19% ($p = 0.02$) respectively; after the 2nd dose by 9% ($p = 0.04$) and 32% ($p = 0.02$) respectively; and after the 3rd dose by 7% ($p = 0.3$) and 23% ($p = 0.06$) respectively. At the end of treatment, there was an overall reduction in blood volume of 33% from baseline ($p = 0.04$). Increase in permeability after RT correlated to subsequent reduction in blood volume after CA4P ($r = 0.76$, $p = 0.004$).

Conclusion: Weekly CA4P with RT caused a sustained reduction in tumour blood volume that is measurable using p-CT. Repeated doses of CA4P resulted in additional decrease in blood volume. Changes in tumour permeability after RT may predict for subsequent tumour response to CA4P. There is potential synergy between CA4P and RT.

1163 POSTER

Relation between P53 codon 72 polymorphism and somatic P53 gene mutation in non-small cell lung cancer (NSCLC)

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Background: *P*53 gene mutation is among the most frequent molecular abnormalities in lung cancer and is strongly associated with cigarette smoking. A relation between *P*53 gene polymorphism and mutation was postulated recently in breast carcinoma but data on this subject in NSCLC have been scarce. The aim of this study was to assess the association between constitutional pro72codon polymorphic variant of *P*53 gene and the risk of somatic *P*53 gene mutations in NSCLC.

Material and methods: Study group included 240 NSCLC patients (52 females and 188 males) who underwent curative pulmonary resection between 1996 and 2000. Arg72Pro *P*53 polymorphism analysis was performed using peripheral blood samples. In 31 NSCLC cases for whom blood samples were not available, tumor-free lung tissue was used for polymorphism analysis. *P*53 gene codon 72 polymorphism was evaluated by allele specific amplification-polymerase chain reaction (ASA-PCR) with Taq DNA polymerase and allele-specific primers. The results were confirmed by denaturing high-performance liquid chromatography (DHPLC). Somatic *P*53 mutation analysis included sequencing of exons 5–8 in tumor DNA.

Results: The frequencies of *P*53 gene Arg72Pro genotypes (Arg/Arg, Arg/Pro, Pro/Pro) in NSCLC patients were 46%, 50% and 4%, respectively. No relationship was found in NSCLC patients between polymorphic variants and clinical characteristics, such as age, sex, pT, pN, histological type and smoking, and neither was there a correlation between polymorphic variants and overall survival. *P*53 gene somatic mutations were found in 76 out of 240 NSCLC patients (32%). Most common were missense mutations. There was no correlation between *P*53 somatic mutations and overall survival. The mutations were more frequent in pro72codon carriers (49/130 patients – 38%) than in arg72codon homozygotes (27/110 patients – 25%). The odds ratio for mutations of *P*53 gene in tumor cells in Pro allele carriers was 1.80 (95% CI: 1.03–3.16).

Conclusions: Arg72Pro *P*53 gene polymorphism may increase the risk of somatic *P53* gene mutations in NSCLC patients. The biological significance of this finding warrants further studies.

1164 POSTER

Can brain metastases (BM) timing presentation influence on survival in patients with lung cancer treated by radiosurgery (RS) ? Long term results

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Purpose: To determine if BM timing presentation (synchronous vs. metachronous) in patients affected of lung cancer treated by RS can influence on overall survival (OS).

Patients and Methods: One hundred consecutive patients (p) have been included; 10% of cases had SCLC. Synchronous BM were observed in 43 cases, and metachronous in 57cases. KPS were as follows: 10 p had 60, 23 p had 70, 34 p had 80, 23 p had 90, and 10 p had 100. Only in 6 p primary tumour was considered in progression. RTOG RPA classes were: class I 31 p, class II 59 p, and class III 10 p. Ninety one percent of patients received WBI (sequential in 63 p). Number of BM previous RS were: one in 59 cases, two in 29 cases, three in 8 cases, and four in 4 cases. Median treated BM volume for RS was 2.7 cc (0.1–23.8). RS doses administered at isocenter was: 22.6 Gy (19–27.3).

Results: median follow-up was 19 m (2–124) (6% lost of follow-up); 28 p were alive at the end of analysis. KPS at last F-U was: 40–60 in 13 p, 70–100 in 14 p, and unknown in 1 p. Median survival time since RS was 10.3 months.

Local control at final analysis: 40 cases (11% in CR) did not progress in brain, 46 progressed, and 14 can not be evaluated because of rapid lethal events. Six patients received RS again as a salvage treatment.

Causes of death: 25 p because brain progression, 26 p because systemic progression, 17 p both causes, 1 p due to intercurrent disease, and 3 p with unknown reason.

On multivariate analysis we observed, as independent prognostic variables for OS, progression of the primary tumour (RR 4.38, CI 1.7–10.9), KPS 60–70 (RR 2.32, CI 1.4–3.9), and absence of WBI (RR 2.8, CI 1.1–6.9).

When we performed an exclusive analysis for NSCLC patients, MST was 10.6 months, and multivariate analyses showed that progression of the primary tumor (RR 4.87, CI 1.7–13.5), and KPS 60–70 (RR 2.16, CI

1.2–3.6) were independent prognostic variables for OS. Timing of BM presentation was not significant for OS (RR 1.83, CI 0.8–3.7).
Relevant side effects were as follows:, corticoesteroids toxicity in 3 p, MRI with leukoencephalopathy/radiation necrosis in 11 p, hidrocephalus in 3 p, stroke in 2 p, and neuro-cognitive symptoms (moderate/severe) in 10 p.
Conclusions: 1. No differences in survival were observed if we consider timing of BM presentation. 2. For the global series low KPS, progression of the primary tumor, and no WBI treatment influenced on survival. 3. For NSCLC patients, MST and prognostic factors were similar.

Publication
Lung cancer

1165 PUBLICATION

Second-line treatment with pemetrexed following platinum based doublet chemotherapy in Malignant Pleural Mesothelioma

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Background: The most widely used first-line chemotherapy regimens in Malignant Pleural Mesothelioma (MPM) are platinum based doublet regimens, with pemetrexed plus cisplatinum being the reference treatment. There is however no universally agreed standard for second line treatment following failure to first line treatment. Pemetrexed has previously shown activity as single agent in first-line treatment with a 14% response rate. It was thus the purpose to evaluate the activity of pemetrexed in second-line treatment of MPM pts without prior exposure to this agent.
Material and methods: Pts had MPM and had disease progression after previously first-line treatment with cisplatinum plus vinorelbine. They received 0.4 mg folic acid PO q d and 1 mg vitamin B12 IM q 9 weeks, both starting one week before chemotherapy. Pemetrexed 500 mg/m^2 was administered as a 10 minutes intraveneous infusion q 3 weeks. Standard prophylactic antiemetic treatment using prednisolone, 5-HT3 receptor antagonists, and metochlopramide was given for 3 days in each course.
Results: A total of 17 patients were included since March 2004. There were 15 males (88%), histologic subtypes were epithelial in 13 pts (76%), biphasic in 3 (18%), and sarcomateous in 1 (6%). IMIG stages II, III, and IV occurred in 1, 8, and 8 pts, respectively, and median age was 63 yrs (range 30–72 yrs). A total of 82 treatment courses have been delivered, with a median of 5 (range 1–9). CTC grade 3 or 4 toxicity was only observed with respect to leucopenia (2 pts had grade 4) and thrombocytopenia (1 pt had grade 4). There was one case of febrile leucopenia, and with fatal outcome. Three partial responses were observed (response rate 18%), time to progression was in median 17 weeks, and median survival 19+ weeks (range 5–45+ weeks).
Conclusions: Pemetrexed has a noteworthy activity as second-line treatment in pts with MPM and progression following platinum containing first-line treatment. There was one toxic death during febrile neutropenia, but the treatment was in general well tolerated. Pemetrexed may be considered for second-line treatment to MPM patients without prior exposure to this agent.

1166 PUBLICATION

Effect of second-line chemotherapy on survival of patients with advanced non-small cell lung cancer pre-treated with docetaxel-based front-line chemotherapy: a retrospective survival analysis.

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Purpose: The effect of second-line chemotherapy (S-LCh) on the survival of patients with advanced non-small cell lung cancer (NSCLC) was retrospectively evaluated in a cohort of patients enrolled different in prospective clinical trials of the Hellenic Oncology Research Group (HORG).
Patients and Methods: Six hundred and thirty-four patients with inoperable stage IIIB or IV NSCLC enrolled on different first-line chemotherapy trials during the period 1995–2000 were analyzed. S-LCh was administered in the context of different ph II HORG'S trials. Patients who did not received S-LCh were considered as "best supportive" control group. Patients' survival was studied with respect to the administration of S-LCh (S-LCh group) or best supportive care (BSC group). Survival was calculated both from the day of starting first-line chemotherapy (OS1) and from the day of first-line treatment failure or the initiation of S-LCh (OS2) until death.
Results: Two hundred twenty-four patients comprised the S-LCh group and 410 the BSC group, respectively. There were significant differences between S-LCh and BSC groups in terms of age, histology, early discontinuation of first-line chemotherapy and performance status after first-line chemotherapy. Three (1.3%) complete and 25 (11.2%) partial responses to second-line chemotherapy were observed for an overall response rate of 12.5% (95% CI: 8.2%-16.8%). The median OS1 was 13 and 7 months ($p < 0.001$) and the OS2 7 and 3 months ($p < 0.001$) for the S-LCh and BSC groups, respectively. In Multivariate analysis revealed that response to first-line chemotherapy, early termination of first-line chemotherapy, performance status and disease stage after first-line chemotherapy, and administration of S-LCh had an independent significant effect on both OS1 and OS2.
Conclusions: Taken into account the limitations of a retrospective study, the presented data support the hypothesis that second-line chemotherapy in patients with NSCLC is associated with a survival benefit.

1167 PUBLICATION

Adjuvant chemotherapy (CT) and patient compliance in non-small cell lung cancer (NSCLC). A multivariate analysis of 356 consecutively treated patients

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Introduction: After the recent Publication onlyn of the positive results of some large randomized trials, a growing interest was noticed for platinum based adjuvant CT after radical surgery in NSCLC. The patient compliance to CT has been equally noticed as an important issue, in the recent and previous studies, with an average of 50% of patients receiving the intended number of CT cycles.
Patients and methods: We retrospectively evaluated the compliance to adjuvant CT for a series of 356 consecutively treated patients, during 1994–2003. All patients had macroscopic and microscopic radical resection of the primary tumor, with or without mediastinal node dissection or sampling, had received at least one adjuvant CT cycle, with or without post-operative irradiation (RT). The CT was planned to be delivered for 6 cycles. The following schedules were used: cisplatin 60 mg/m^2, cyclophosphamide 600 mg/m^2 and epirubicine 50 mg/m^2 on day 1(16%), etoposide 120 mg/m^2 + cisplatin 30 mg/m^2, both intravenously on days 1–3, every 21 days (68%), other platinum based (16%). A multivariate analysis, for a target of 4 and 6 cycles, was performed in order to evaluate the impact of the following categories: age, sex, extent of surgery, stage, RT, patient residence.
Results: One hundred seventy nine patients (50%) completed all 6 cycles, while 299 (84%) received at least 4 cycles. The medium number of administered cycles was 5.
The multivariate analysis of patient characteristics on treatment compliance is shown in the table bellow.

Characteristic	Total	4 cycles			6 cycles		
	-	%	OR (95%CI)	p	%	OR (95%CI)	p
Age[a]			0.99 (0.96–1.02)	0.63		0.97 (0.95–0.99)	0.01
Gender							
M	289	85	0.78 (0.38–1.58	0.49	52	0.65(0.37–1.14)	0.13
F	67	81			42		
Surgery							
Pneumectomy	129	83	0.83 (0.44–1.58)	0.58	43	0.54 (0.33–0.87)	0.01
Lesser resection	227	85			54		
RT							
Yes	147	86	0.52 (0.31–1.10)	0.10	50	1.04 (0.66–1.63)	0.84
No	209	77			49		
Residence							
Local	164	81	0.67 (0.37–1.20)	0.18	46	0.75 (0.49–1.16)	0.20
Remote	192	86			54		
Stage							
I, II	149	84	0.90 (0.48–1.70)	0.75	51	1.17 (0.73–1.82)	0.51
III	207	83			51		

[a]Age used as a continuous variable. OR: odds ratio, CI: confidence interval.

Conclusion: Using the above mentioned combinations, the patient compliance with adjuvant CT was good, with 84% receiving at least 4 and 50% all 6 cycles. The medium number of cycles was 5. For a target of 4 cycles none of the investigated variables had a significant impact. For a longer CT duration, age and extent of surgery were correlated with a lower compliance.