CANCER DE PULMON

Circular inicial preparada en Marzo 2001. Algoritmo Nov 2007.

Aplicaciones de biología molecular

Marcador diagnostico	c-myc (SCLC 15-44%)
Marcador diagnostico	c-myb (SCLC 87%, NSCLC 30%)
Marcador diagnostico	ras mutado (controversia en relacion a pobre supervivencia)
Marcador diagnostico	raf-1 (comun en SCLC & NSCLC)
Marcador diagnostico	GRP-bombesin (SCLC), proGRP (gastrin releasing hormone)
Marcador diagnostico	Chromogranin A (SCLC)
Marcador diagnostico	Rb (SCLC 90%) o del p16 (Todos SCLC presentan)
Marcador diagnostico	EGF (NSCLC)
Marcador diagnostico	MoAb DF-L1 (contra LCAP Lung Cancer Assoc Protein)
Marcador diagnostico	LOH 17q (NSCLC 42%)
Marcador diagnostico	LOH RAR B o G (NSCLC 40-70%)
Marcador diagnostico	COX-2 hiperexpresado en adenoca y lesiones precursoras
Marcador diagnostico	Scatter factor aumentado en bronquioloalveolar solamente
Marcador diagnostico	IL10 & IL10R presente en mayoria de NSCLC (baja inmunid)
Marcador diagnostico	N-CAM , >20u/mL, + 50% SCLC (solo 34% NSE).

Marcador mal pronostico	LOH 5q21, APC/MCC (NSCLC 30%)
Marcador mal pronostico	Microvasculatura
Marcador mal pronostico	alter p16 (NSCLC 51%)
Marcador mal pronostico	p53 mutado (enf extensa y mala respuesta a CDDP)
Marcador mal pronostico	proliferación (Ki-67, PCNA, aneuploidia, timidina)
Marcador mal pronostico	elevación citokinas (G-CSF, GM-CSF, M-CSF, IL6)
Marcador mal pronostico	p27kip-1, NSCLC marcador de recaida postoperatoria
Marcador mal pronostico	citoqueratina 19, CK 18, 1p13-q21, 9p13-q13
Marcador mal pronostico	pakoglobin (cadherin) (NSCLC 45%)
Marcador mal pronostico	microsatelitosis presente en plasma (50%). Enf residual.
Mal pronostico y ausencia de respuesta a CDDP	Metilacion de 14-3-3d

Respuesta a quimioterapia	Serpin B3 Quimioresistencia en SCC y efecto paradoxico favorable en adenocarcinoma.
Respuesta a quimioterapia	Reducción de Ab-p53 despues del tratamiento (NSCLC)
Resistencia a quimioterapia	HER2/neu (NSCLC 30%)

Supervivencia pobre	del 3p14-23 (FHIT, target de tabaco) (SCLC 90%, Otros 30%)
Supervivencia pobre	elevación PAI-1
Supervivencia pobre	expresión baja Integrina alfa-3 (en adenocarcinoma)
Supervivencia pobre	metilacion DAP (Death Assoc Protein) en NSCLC
Supervivencia pobre	LDH y Na discriminan supervivencia en SCLC-Ltd Disease
Supervivencia pobre	Hepatoma derived growth factor

Supervivencia buena	MRP1 (CD9) & KAI1 (CD82) identifica N0 en NSCLC
Supervivencia buena	KAI-1 supresor de metastasis en NSCLC
Supervivencia buena	MIA15-5 (contra HLA A & B). La negatividad es favorable (NEJM 1992;327:14-8)
Supervivencia buena	bcl-2 (NSCLC 25%)
Supervivencia buena	p21-TGFB-1 aumentada en NSCLC
Mejor supervivencia	Aumento expresion de RRM1 y PTEN en NSCLC
Mejor supervivencia	HTERT >15ng/mL
Supervivencia buena	p21-TGFB-1 aumentada en NSCLC
Supervivencia buena	Normalizacion NSE a 4 sem (SCLC)
Significado desconocido	expresión alta de FAS-ligand
Significado desconocido	Telomerasa, presente en 90%
Significado desconocido	bcl-2 + (50% SCLC)
Marcador de tabaquismo	DRD2 (polimorfismo de dopamina reward gene)

EGFR overexpression 33%, HER2 overexpression 34%, both 16%. Correlated with poor prognosis in surgically resected patients.

E Cadherin and catenin (a, b & g) correlate with dedifferentiation, invasion and metastases leading to a reduced survival.

Hepatoma derived growth factor (HDGF) present in NSCLC. IN Stage I patients t5hose above the mean (185±41) had 5 y OS 26 vs 82% and 5 y DFS 42% vs 92%…

Favorable prognosis related to p16,p21 & p27. Unfavorable prognostic factors cyclin B1, cyclin E, surviving, VEGF, collagenXVIII. Rb failed, and Cyclin D1 and Bcl2 were equivocal.

HER2 increase measured by FISH present in 22.8% correlated with OR 34.8% compared to normal HER2 only 6.4%, and had better disease control rate (56.5% vs 33%), MTTP 9.05 mo vs 2.7 mo, and OS 20.8 mo vs 8.4 mo. When HER2 associated with EGFR mutation had better outcome…

Rs1862214 single nucleotide polymorphism (GG or CG, compared to the common genotype CC)) of PDCD5 gene (programmed cell death 5) increased lung cancer risk in smokers (HR 1.9) and presented with worst clinical stage (HR 1.8).

Matrix metalloproteinase variant G allele MMP-2 1082 A/G associated with poor survival in stage I NSCLC (HR 1.94 for OS).

W Franklin et al (Sem Oncol 2002;29:3-14) Sequence events in lung carcinogenesis: Normal - (LOH 3p, 9p) - hyperplasia - (growth factors)- Squamous metaplasia - (loss of apoptosis via PI3K, Akt; proliferation myc, jun, ras) - Dysplasia (p53) - Ca in situ, Invasive carcinoma. (Role for methyl p16, O6MGMT, RARB promoters…)

**A Maeshima et al (Cancer 2002;95:2546-54). Scar grade in small peripheral adenocarcinoma of the lung: Grade I: no desmoplasia (with/out collapse) 10 y OS 100%; Grade 2: sparse desmolastic reaction (83%); Grade 3: Dense desmoplastic

reaction of <10mm diameter (52%); and Grade 4: Dense desmoplastic > 10 mm diameter (37.5%).

***K Yanagisawa et al (Lancet 2003;362:433-9). Proteomic patterns identified by MALDI-TOF MS with profile of proteins up to 50 kDa. Used in 50 tumors distinguished squamous form adenocarcinoma and tumor vs normal lung with a sensitivity of 100% and predicted 5 y OS groups OF 50% AND <5% after surgical resection (50% cases).

H Endon et al (JCO 2004;22:811-9). Selected 8 genes out of 44 detected as prognostic markers of adenocarcinoma (Garber et al PNAS USA 98;13784-9, 2001 and Bhattachorjee et al PNAS USA 98;13790-5, 2001): PTK 7 (HR 0.5), CIT (HR 0.6), SCNNIA (HR 1.7), PGES (HR 2.2), EST-LB4D (HR 1.9), ERO 1l (HR 0.2), EST-AA434256 (HR 0.4) and ZWINT (HR 2.3). Low risk group had a 85% 5 y OS and high risk 40% 5 y OS.

*********C French et al (JCO 2004;22:4135-9). Midline carcinoma of children and young adults (median age 32 yo) present with NUT oncogene fusion t(15;19), single chromosomal translocation. Poor prognosis in 50%. Should be considered a new entity with primaries in H&N, thymus, lung.

MUTACIONES EGFR

***S Kobayashi et al (NEJM 2005;352:786-92). Most common mutation of EGFR is L858R or a small deletion 747-750. After 2 y CR to Iressa progression is associated to a second mutation structurally equivalent ot Gleevec bcr-abl mutation which abrogated a CR in CML: Threonine to methionine change at 790 EGFR position. An analog CL-387.785 has been identified to overcome this resistance in the T790M mutation. Brilliant.

A Shigematsu et al (JNCI 2005;97:339-46). EGFR mutation found in 130/617 NSCLC (21%) in an international study: mutations were: in frame in exon 19, single missense mutation in exon 21, in frame duplication/mutation in exon 20. K-ras mutations fpund in 8% (50/617) and none of them had EGFR mutation. EGFR mutations related to never smokers (51% vs 10%), adenocarcinoma (40% vs 3%), East Asians (ancestry also important since asians in Australia and USA had higher frequency) (30% vs 8%), and females (42% vs 14%), and were not associated with age, stage, brochioalveolar histology or OS.

***W Pao et al (JCO 2005;23:2556-68). Up to Novc 04 detected 192 EGFR mutations 85% in two spots: 55.8% LREA 19 del and 44.2% L858R exon 21 point mutation. Activation leads to oncogene addiction by continuous growth stimulation. PCR based assays are available.

****F Cappuzzo et al (JNCI 2005;97:643-5). High EGFR gene copy identified by FISH dorrelates with response to Gefitinib better than mutation of EGFR. EGFR amplification is related also to OR 36% vs 3%, disease control rate 67% vs 26%, TTP 9

mo vs 2.5 mo, and OS 18.7 mo vs 7 mo. Mutation of EGFR correlated with OR and TTP but not OS.

RK Thomas et al (Clin Ca Res 2006;12:4384S-91S). EGFR mutations: 45% 19del, 40% L858R, very sensitive to Iressa, 5% G719S.

S Toyooka et al (Ca Res 2006;66:1371-5). N=164 adenocarcinoma. Two pathways: First type characterized by EGFR lower expression in p16/CDH13 methylation cases and viceversa less methylation in EGFR mutation cases; and second type with k-ras mutation in p16 methylation cases.

MICROARRAYS

H Endon et al (JCO2004;22:811-9). Selected 8 out of initial 44 genes for adenocarcinoma (Garber et al PNAS USA 98:13784-9; 2001) and Brattacharjee et al (PNAS USA 98:13790-5;2001). Low 5 yOS 85% (N=42) and high 5 yOS 40% (N=43).

DN Hayes et al (JCO 2006;24:5079-90). Gene expresión by DNA microarrays in lung adenocarcinoma distinguished 3 groups (bronchoid, squamoid and magnoid) with distinct clinical characteristics (BAC, epidermoir and large cell variants).

HY Chen et al National Taiwan Univ Hosp-7 (NEJM 2007;356:11-20). Microarray analysis identified a 5 gene signature (DUSP6, MMD, STAT1, ERB-B3, LCK) for RT-PCR decision tree analysis in operable lung cancer (no adjuvancy). Low risk 2 y OS 95% vs 50% in high risk signature in stage I, and 70% vs 30% in stage II. MST 40 vs 20 mo, MRFS 29 mo vs 13 mo.

M Skrzypski et al R Rosell (ASCO 2007). 29 genes array RT-QPCR identified tumor >4cm and high risk genes (CSF1, EGFR, CAIX). N=66. SCC risk score: 0.93 x CSF + 1.4 x CAIX + 1.1 x EGFR. Low score MST > 40 mo; high score MST 21.1 mo.

***M Seike et al (JNCI 2007;99:1257-69). 17 cytokine gene expression in lung adenocarcinoma/non cancerous tissues. From these 11 genes classified for risk of death (predictive even in stage , also predicting ly no mets). HR=7.46. (IL10, IL8, IL6, INFa, IL15, IFNg, IL1a, IL1b, IL12p35, CSF1... most of them high in non tumor tissue)

PREDICCION DE RESPUESTA A QUIMIOTERAPIA

Z Zheng et al (NEJM 2007;356:800-8). N=187. Immunohistochemistry study of RRM1 (nucleotide excision repair) and ERCC1 (DNA excision repair complex). Both + in 30%, and shared an excellent prognosis 5yOS >80% in surgical cases. Since ERCC1 indicates resistance to CDDP/GEM is difficult to explain the goor proghnosis but certainly indicates no need of adjuvant chemotherapy.

M Cobo et al R Rosell (JCO 2007;24:2747-54). N=444. ERCC1 mRNA evaluation and then randomized to control TXT+CDDP vs genotype directed: Low ERCC1-TXT+CDDP; high ERCC1 TXT+GEM. Results: OR 39.3% control and 50.7%

genotype. MST both 9.8 mo. Propose low ERCC1 CDDP+GEM

G Simon et al (JCO 2007;25:2741-6). Selected patinets according to RRM1 low (GEM) or high (TXT; and ERCC1 low (CBDCA) or high NVB. OR, OS and PFs no differences. OR 44%, 1yPFS 14%; 1yOS 59%. Crossover similar results. In any case very poor results...

T Fan et al (Ca Res 2007;67:7901-6). 14-3-3c oncogene expression correlated with poor prognosis in adneocarcinoma of lung and also for resistance to CDDP (Low expression better response to CDDP).

NON SMALL CELL LUNG – BRONCHIOLOALVEOLAR CANCER

J Zell et al (JCO 2005;23:8396-405). New definition by WHO in May 1999 restricted BAC to tumors without invasion, only bronchioloalveolar growth. End results changed with MOS improving from 32 to > 53 mo, while there were no changes in the other adenocarcinoma types. Adenocarcinoma with BAC features without foal invasion is excluded from BAC.

DJ Rag et al (Clin Ca Res 2006;12:3698-704). BAC surgery 5 y OS 50-70%, local recurrence 50%. Differences in gene expression were: Pure BAC Survivin +++, A Cathenin ++, E Cadherin +++, Laminin -, k ras + p 53 +; Mixed BAC Laminin +, A catenin ++, E cadherin +, p53 +; Mucinous BAC p53 -, k ras +++; Adenocarcinoma p 53 ++, kras +.

L West et al (JCO 2006;24:1807-13). Gefitinib 500 mg qd. N=136. M age 68 yo, 71% female, 89% PSK 0-1. OR 17%, 6% CR untreated (N=69); OR 9%, 0 CR treated (N=22). MST 13 mo, 3 y OS 23%. 2% dead due to interstitial lung disease.

PREVENCION PRIMARIA: TABAQUISMO

El estudio Hutchinson Smoking Project (en escuelas de US, Seattle) ha demostrado no efecto. Ha sido bien diseñado y realizado y demuestra que no se afectan los habitos del tabaco (JNCI 2000;92:1979-91).

***N Rigotti et al (NEJM 2002;346:506-12). Tobacco use and dependency is a chronic disorder requiring conseling and pharmacotherapy. Nicotine replacement 8 wk – 6 mo (Transdermal poatch, gum, inhaler, nasal spray) + sustained release bupropion 150 mg/d x 3 then 150 mg bid x 2-6 mo , an dconseling and follow up.

C Haiman et al (NEJM 2006;354:333-42). African Amer/ Hawaians > Whites regarding lung cancer in groups with <1 pack/day; differences lñost with >1.5 packs/d.

****G Goodman et al (JNCI 2004;96:1743-50). Beta carotene 30 mg + Retinyl palmitate 25.000 iu q d. N=18.314 high risk tobacco/asbestos. Adverse side effects

prompted early discontinuation. Excess risk of lung cancer 1.12 and cardiovascular death 1.08 at 6y. Negative study.

DIAGNOSTICO PRECOZ-PREVENCION SECUNDARIA

Claudia Henschke et al (Lancet 1999;354:99-105). Encontraron mediante TAC helicoidal de alta resolución que 233/1000 pacientes con alto riesgo y >60 años, tenian lesiones nodulares no calcificadas (la placa simple de torax vio solamente 7%). La repetición a los 3 meses y/o la biopsia, si era de 6-10 mm, demostraron tumor en 2,7%. 26/27 tumores eran T1 resecables. (Los datos son al menos x4 los obtenidos en screening de cancer de mama, pero la población ha sido muy seleccioinada y no hay controles).

Diagnostico precoz de lesiones premalignas con Laser Induced Fluorescence Bronchoscopy (LIFE)

Mulshine et al señalan que el MOAb 703D4 (contra hn RNP A2/B1 -heterogeneous nuclear ribonucleoprotein) es util en el diagnostico precoz del cancer de pulmon, con sensibilidad 96% y especificidad 86%. Lo recomiendan conjuntamente con la detección de k-ras, p53, inestabilidad genomica y metilacion de p16.

Quimioprevencion:
Utilización de 5'aza-2'deoxycytidine para restaurar la expresión de genes metilados en las etapas iniciales de carcinogenesis (como quimioprevencion en casos de riesgo):
Metilacion de RAR Beta en 72% SCLC y 41% NSCLC.
Metilacion de FHIT en 100% SCLC y 65% NSCLC

IL2 inhalada previene 65-80% la aparicion de cancer de pulmon en modelos murinos!. (Buscar referencia con L´Herminier ¿?)

M Melamed (Cancer 2000;89:2356-62). NCI-NY Study with 10.000 male (MSKCC, JHUH Baltimore and Mayo Clinic), > 45 yo, smoking, 2 y F up: Randomized to Cytology q 4 mo + Chest XR q 1 y (Initial lung cancer 30 –9 only cytology- and later 175 cases) and only chest XR (initial 23 AND LATER 175). Stage I 40%, 5 y OS 35% (historically USA Series 13%). Recommended.

C Henschke et al (Cancer 2001;92:153-9). Follow-up repeat screening of the initial 1000 high risk individuals. Initial findings 2.7% malignant tumors (83% not visible in the chest X.Ray), 2.3% Stage I. Follow up CT positive 2.5%: 2 deaths, 12 resolved, 16 no growth, 8 documented growth (6 NSCLC: 5 Stage IA, 1 Stage IIIA & 1 SCLC; median size 8 mm), and another 2 patients had further studies showing 1 NSCLC Stage IIB and 1 SCLC limited disease. Recommend annual CT study.

G Strauss (JCO 2002; 21: 1973-83) Mayo Clinic Project Cohort, N=9192. Mortality was increased in experimental group (screen with chest XR/cytology) due to increased cancer incidence (HR 1.3). Early diagnosis lead to a 50% cure rate due to resection.

Survival was then improved in the screening group 5 y OS 29% vs 13% (plateau). Survival rather than mortality provided an unbiased surrogate for cure.

U Pastorino et al INT Milano (Lancet 2003;362:593-7). N=1035, >50 yo, 20 y/pack, annual CT±PET x 5 y & lesions < 5 mm repeat at 1 y. On second year: 22 lung cancer (11 base line and 11 at year 2). 29% participants had lung lesions (440 lesions/298 participants). PET + in 18/20 cancer cases. 6 false positive with benign diagnosis (6% of recalls and 22% of surgery cases). Complete resection 95%; stage I 77%, mean size 18 mm. Lesions < 5 mm can be delayed.

G Bepler et al (Ca Control 2003;10:306). CT screening of interest in > 60 y o with moderate smoking and without other medical problems. Pathologic CT 23.3%, cancer 2.7%.

******International Early Lung Cancer Screening C Henschke et al (NEJM 2006;355:1763-71) N=31.567. First round 320 and second round screen 55. Stage I 412 (85%); 10 y OS 88% (operated first month 92%, and 8 patients without therapy, none survived 5 y). High risk >60 yo, former/current smokers give a 1.3% baseline & 0.3 annual screening (better than breast in >40 yo, with a 0.6-1% baseline & 0.2-0.4% second screen). Cost effective

ESTUDIOS DE EXTENSION

En estadio locoregional , IIIB, la presencia de derrame pleural cambia la supervivencia significativamente (MST 15 me vs 7 me)

P De Leyn et al (JCO 2006;24:3333-9). N=30, Stage IIIA, N2, mediastinoscopy +. Neoadjuvant Rx then restage with PET-CT and mediastinoscopy. At thoracotomy 17 had N2+. PET-CT sensitivity 77%, specificity 92%, accuracy 83% and remediastinoscopy sensitivity 29%, specificity 100% and accuracy 60%.

TW Generts et al (Clin Ca Res 2005;11:6608-14). Criteria to distinguish second lung primary vs metastatic head and neck cancer are base din stage of H&N cancer at presentation, central or peripheral location of lung mass & single or múltiple nodules, and finally time interval more or less than 3 years. In a series of N=44, according to classical clinical criteria 38 were mets and 6 primaries. By PCR LOHP analysis 24 were concordant (mets) and 18 were primaries. Interest in surgery…

NSCLC – LOCALIZED COMBINED THERAPY

NK Altorki et al (JCO 2003;21:2645-50). Neoadjuvant treattment in stages IB-IIIA. TXL + CBDCA + Celecoxib 400 mg bid. OR 65% (CR 17%,), 28/29 surgery, 24% minimal disease. PGE2 levels decreased in the tumor. Results suggested increase ij CR.

***International Adjuvant Lung Cancer Trial Group (NEJM 2004;350:351-60). Complete resected patients N=1867, 36% Stage I, 39% stage III, M F up 56 mo.

Randomized to CCDP based ChX (5 y OS 44.5%, 5 y DFS 39.4%) vs Observation (5 y OS 40.4%, 5 y DFS 34.3%). New standard of care.

K Hotta et al (JCO 2004;22:3860-7). Meta-analysis of Adjuvant ChX in resected NSCLC, 11 trials, N=5716 patients. HR 0.872, CDDP based HR 0.891, Uracil-Tegafur based HR 0.799.

K Pisters , T Le Chevalier (JCO 2005;23:3270-8). Review prior trials and 7 recent ones on >4000 patients with adjuvant platinum based and recent doublet combinations, showing a 5 y increase in OS 5-18%, representing a new standard of care for Pt based chemotherapy.

B Jeremic et al (JCO 2005;23:1144-51). N=64, stage III. Treatment: TXL 30 mg/m2 d1, Then Hyperfractionated RT 1.3 Gy bid uo to 67.6 Gy, & daily CBDCA 25 mg/m2 + TXL 10 mg/m2 between XR doses. OR 83%, CR 42% + PR 41% + NC 16% + PD 2%, MST 28 mo, 3 y OOS 37%, 5 y OS 26%, MTTP 25 mo, 5 y Distant-Mets-DFS 31%.

***SG Divers et al (JCO 2005;23:6664-73). First CDDP+GGEM x 2; then TXL 35 mg</m2 wkly x 7 + GEM 150 mg/m2 wkly x 7 + RT 60 Gy (had tro be reduced due to toxicity). OR prior to RT 49%, after RT 75% (94% in wkly TXL); MOS 23 mo, 3 yOS 45%, Local relapse 20%.

J Bradley et al RTOG 9705 (JCO 2005;23:3480-7). Adjuvant postoperative treatment 8 wk after surgery, stage II-IIIA. TXL 135 mg/m2 + CBDCA AUC 5-6 q 3 wk x 4 + RT 50 .4 GY (28F)/6 wk. Results: 93% completed RT, 86% completed ChX. MOS 56.3 mo, 3 y OS 61%, 3 y PFS 50%, local failure 15%. Improved historical series.

BE Lally et al (JCO 2006;24:2998-3006). Postoperative RT according to SEER Database: N=7465, M F up 3.5 y. N2: survival HR 0.855, N0 HR 1.17, N1 HR 1.09.

***JP van Meerbeck et al EORTC (JNCI 20076;99:442-50). Unresectable NSCLC IIIA, N2. Neoadjuvant Chx CDDP based x 3; OR 61% (N=579). Randomized to Surgery (154/167 operated, 50% resected, 5%CR, 4% deaths and 40% postopRT) or Radioterapy (Completed 55%, late severe toxicity 4-7%). MST 16.4 vs 17.5 and 5yOS 15.7% vs 14%. RT consolidation is therefore the preferred modality.

T Seiwert et al (Clin Ca Res 2007;13:515-22). N=30. Alimta 500 mg/m2 + CBDCA AUC 5-6 + RT 40-66 Gy. 4 CR + 8 PR. Esophagitis, myelotoxicity.

**P Garrido et al R Rosell (JCO 2007;25:4736-42). N=136, N2 & IIIB T4-N0-1. Neoadjuvant CDDP+GEM+TXT x 3 and then surgery. OR 56%; Complete resection 68.9% (72% IIIA and 66% IIIB); pCR 12.9%; mortality 7.8%; MOS 15.9 mo; 5yOS 21.1%. MST 48.5 mo for completely rescted, 12.9 mo for incomplete resections and 16.8 mo for non resected. 5yOS 41.4 % complete resection and 11.5% incomplete resection, 0% non resected.

T Seiwert et al (Clin Ca Res 2007;13:515-22). N=30. Alimta 500 mg/m2 + CBDCA AUC 5-6 + RT 40-66 Gy. OR:4 CR + 8 PR. Esophagitis and myelotoxicity.

NSCLC ADVANCED -CHEMOTHERAPY

C Kosuras et al (Cancer 2000;89:774-82). N=50, Phase II. TXL 175 mg/m2 + IFX 5 g/m2 + CDDP 100 mg/m2. OR 64% (4CR), QOL improvement 74%, MDR 7 mo, MTTP 8 mo, 1 y OS 53%.

J Schiller et al ECOG (NEJM 2002;346:92-8). N=1155, >80% stage IV, med age 62 yo. Randomize dto CDDP+TXL (2 y OS 10%) vs CDDP + TXT (11%), vs CDDP+GEM (13), vs CBDCA+TXL (11%). No differences. Very slight improvement in 2 y OS. MST 7.8 to 8.1 mo.

J Hainsworth et al (JCO 2002;20: 2937-42). N=321, M F up 58 mo. Phase II CDDP+TXL and a third agent VNR or GEM. MOS 8.6 mo, 2 y OS 19%. No differences according to third agent.

M Socinski et al (Cancer 2002;95:1520-7). N=40. CPT 100 mg/m2+ TXL 175 mg/m2 + CBDCA AUC 5. OR 32%, MTTP 5.3 mo. 2 y OS 21%.

Iressa ZD1839, **FDA approval** (accelerated aproval as monotherapy in failures to CDP+TXT NSCLC) **on May 5th, 2003** . Second line IDEAL 1 & 2 TRIALS: OR 10-20% NC 30%, MST 6.5 –7.6 mo. OR better for females (17.5% vs 5.1%) and non smokers (28.6%), 75% had adenocarcinoma, MRD 250 mg/d. Diarrhea 50%, rash 50%, pulmonary interstitial fibrosis <!%. INTACT TRIALS no first line OR/MST improvement in combination with CDDP-GEM or CBDCA-TXL. (J Baselga JCO 2004;22:759-61, need of preclinical and early clinical results before large randomized studies).

N Akerley et al CALGB (Cancer 2003;97:2480-6). N=38, No prior RX. TXL 150 mg/m2 in 3 h iv wkly x 6 q 8 wk (high dose). Neurotoxicity >50%, Hematologic toxicity 39%. PR 42%, MST 12.6 mo, 2 y OS 26%.

NK Altorki et al (JCO 2003;21:2645-50). N=29, stage IB-IIIA. Celecoxib 4oo mg bid qd + TXL 225 mg/m2 + CBDCA AUC 6 q 3 wk x 2 then operation: Operated and resected 28/29. No pCR found, 24% micro residual tumor, down staged 13/29. OR 65% (CR 17%). Toxicity hematol 67%. Celecoxib increased OR. Patients showed normal PGE2 levels. Confirmatory trial on going…

Ch Belani et al (JCO 2003;21:2933-9). N=401, Stage IIIB-IV. Randomized to TXL 100 mg/m2 wkly + CBDCA AUC 6 d 1 (OR 32%, MTTP 30 wk, MST 49 wk, 1 y OS 47%) vs TXL 100 mg/m2 + CBDCA AUC 2 wkly x 3 q 4 wk (OR 24%, MTTP 21 wk, MST 31 wk, 1 y OS 31%) vs TXL 150 mg/m2 1st cycle and then 150 mg/m2 cycle 2 + CBDCA AUC 2 wkly x 6 q 8 wk (OR 18%, MTTP 27 wk, MST 40 wk, 1 y OS 41%). At wk 16 maintenance randomized to TXL 70 mg/m2 wkly x 3 q 4 or no RX. First arm best therapeutic index…

***JG Paez et al DFCI (Science 2004;304:1497). Mutation of EGFR 15/58 Japanese tumors and 1/61 USA tumors. Gefitinib response only in mutated cases 5/5 responders when mutation in TK domain and 0/5 responses when no mutation found.

***T Lynch et al MGH (NEJM 2004;350:2129-39). Identified TK domain mutation of EGFR gene in 8/9 patients with Gefitinib responses and in 0/7 non responders.

**V Miller et al MSKCC (JCO 2004;22:1103-9). N=139 on Geftinib. OR 15%. Prognostic factors of the response: Adenocarcinoma 19% vs 0%, Bronchioloalveolar 38% vs 14%, non smoker 36% vs 8%, and KPS>80 22% vs 8%.

**D Johnson et al (JCO 2004;22:2184-91). N=99, Phase II. Randomized to TXL 200 mg/m2 + CBDCA AUC 6 + BV 15 mg/kg (OR 31.5%, MTTP 7.4 mo, OS 17.7 mo) vs CBDCA + TXL (OR 18.8%, MTTP 4.2 mo, OS 14.9 mo). Toxicity minor mucocutaneous hemorrhage and major hemopthysis in squamous cell ca with necrosis and cavitation. Favorable in non squamous cell carcinoma.

**N Hanna et al (JCO 2004;22:1589-97). N=571, second line therapy. Randomized to Alimta 500 mg/m2 d 1 + Vit B12 + FA + DXMTS q 3 wk (OR 9.1%, MOS 8.3 mo, 1 y OS 29.7%) vs TXT 75 mg/m2 + DXMTS d 1 q 3 wk (OR 8.8%, MOS 7.9 mo, 1y OS 29.7%. Equivalent.

C Monnerat et al (Clin Ca Res 2004;10:5439-46). N=60, Untreated, stage III-IV. GEM 1250 mg/m2 d 1 & 8 + Alimta 500 mg/m2 d 8 + FA + Vit B12. OR 15.5%, NC 50%. MOS 10.1 mo, 2 y OS 18.5%, MPFS 5 mo.

H Hotta et al (JCO 2004;22:3852-9). Meta-analysis comparing CCDP vs CBDCA based chemotherapy. 8 trials, 2948 patients. CDDP best OR but survival was equal (HR 1.05). Two drugs better survival HR 1.1 (11% benefit) than CBDCA with same combination agents.

Y Ichinose et al (Clin Ca Res 2004;10:7860-4). S1 40 mg/m2 bid x 21 d + CDP 60 mg/m2 d 8 q 5 wk. N=56. 1 CR + 25 PR (OR 47%), MST 11 mo, 1 y OS 45%.

N Hanna et al (JCO 2004:22:1589-97). N=571. Second line ChX randomized to Alimta, 500 mg/m2 + Vits q 3 wk (OR 9.1%, MPFS 2.9 mo, MST 8.3 mo) vs TXT 75 mg/m2 q 3 wk (OR 8.8%. MPFS 2.9 mo, MST 7.9 mo). Less toxic, no alopecia.

**** D H Johnson et al (JCO 2004;22:2184-91). N=99. Randomized study CBDCA AUC 6 + TXL 200 q 3wk + BV 15 mg/kg (OR 31.5%, TTP 7.4mo, MOS 17.7 mo) vs CBDCA + TXL (OR 18.8%, TTP 4.2 mo, MOS 14.9 mo). Major hemopthysis in squamous cell, cavitated, tumor necrosis and tumor invading major blood vessels…

***T Hoang et al ECOG DATA (JCO 2005;23:175-83). Prediction of OS with third generation regimens. Stage II (effusion) or IV: OR 20%, MST 8.2 mo, 1 y OS 33%, 2 y OS 11%. Factors: Skin mets (HR 1.88) score 66, Lower KPS (HR 1.46) score 43, Loss appetite (HR 1.62) score 38, liver mets (HR 1.32) score 35, >4 bone mets (HR 1.2) score 19, and no prior surgery (HR 1.16) score 15. Adding scores define a four risk groups: Low risk score <40 (1 y OS 40%, 2 y OS 15%); low intermediate score 40-60 (1 y OS 34%, 2 y OS 10%); high intermediate score 60-80 (1 y OS 27%, 2 y OS 6%); high score 80-120 (1 y OS 14%, 2 y OS 2%).

R Herbst et al (JCO 2005;23:2544-55). Erlotinib 150 mg/d po + BV 15 mg/kg q 3 wk. N=40 non squamous cell after prior ChX. OR 20% + NC 65%, MOS 12.6 mo, MPFS 6.2 mo.

****MS Tsao et al NCIC BR.21 (NEJM 2005;353:123-32). Double blind randomized trial second line Erlotinib vs Placebo. N=731, 49% prior Rx, 93% prior Pt ChX. OR 8.9% vs <1%, MDR 7.9 mo vs 3.7 mo, PFS 2.2 mo vs 1.8 mo, OS 6.7 mo vs 4.7 mo. ***** (NEJM 2005;353:133-44). OR to Tarceva related to mutation in EGFR (exon 19 del, and L858R exon 20) Number of copies non related to OR to Tarceva. OR not related to survival benefit…

T Takano et al (JCO 2005;23:6829-37). N=66 . Relapsed after surgery. 39/66 (59%) had EGFR mutation (20 with del 19, and 17 L858R as well as others, and had OR 32/39 (82%) to Gefitinib as compared with only 3/27 without EGFR mutation. MTTP 126 mo vs 1.7 mo, MOS 20.4 mo vs 6.9 mo. Another 29/66 (44%) had increased EGFR copies (>3/cell) and presented OR 72% (21/29) (no overexpression 38% (14/37), MTTP 9.4 vs 2.6 mo.

F Hirsch et al SWOG (JCO 2005;23:561-9). N=81 BAC. Treatment with Iressa 500 mg/d. EGFR+ by FISH (MOS 18+ mo, MPFS 9 mo, OR 63%)) while EGFR- by FISH (MOS 8 m0, MPFS 4 mo, and OR 39%).T Mukohara et al (JNCI 2005;97:1185-94). Ceel lines with EGFR mutation. Compared Gefitinib and Cetuximab indicating better Gefitinib and suggesting a different mechanism of action for Cetuximab.

RL Yanch et al (Clin Ca Res 2005;11:8686-98). Multiarray study indicated that NSCLC cell lines showing epithelioid to mesenchymal transition presented rresistance to Erlotinib, and E cadherin/ catenin correlated with Erlotinib sensitive cell lines

JY Han et al (Cancer 2005;104:2759-65). CPT 90 mg/m2 d 1 & 8 + XEL 1000 mg/m2 bid d 1-14 q 3 wk. OR 41.5%, MOS 14.6 mo. Non toxic.

***KL Reckamp et al (Clin Ca Res 2006;12:3381-8). Celecoxib optimal biological dose 600 mg bid (maximal urinary decrease of PGE-M without toxicity) + Erlotinib 150 mg qd. N=22, OR 7PR (33%) + 5NC (24%), Rash 86%. Decrease PGE-M in 8 wk. 5/17 EGFR mutation all had OR. COX2 inhibitors synergistic with EGFR pathway inhibition.

****K Olanssen et al (NEJM 2006;355:983-91). Reviewed ERCC1 by IHC (8FI, Neomarkers) in tumor biopsies after IALT study indicated CDDP adjuvant therapy improved survival in Stage I-III after surgery in NSCLC. ERCC1 + in 44% (N=335) and negative in 56% (N=426). CDDP OS improved only in ERCC1 negative (HR 0.65), but ERCC1 + patients without CDDP had a better survival (HR 0.66). In ERCC1 negative 5 y OS 47% vs 39%, MST 56 mo vs 42 mo. There was no difference for ERCC1+ due to ChX. 5 yOS for ChX 44% and control 42%.

S Niho et al Chiba Japan (JCO 2006;24:64-9). First line Gefitinib in Japan. N=42. OR 30%. Acne 50%, diarrhea 18%, liver toxicity 8%, fatal pulmonary interstitial disease 10%. MST 13.9 mo, 1 y OS 55%. EGFR mutation detected in 4/13 patients and all had a response.

A Paccagnella et al (JCO 2006;24:681-7). N=324. Randomized sutdy of TXL 200 + CBDCA AUC6 + GEM 1000 d 1 & 8 (OR 46%, MTTP 7.6 mo, MOS 10.8 mo, 1 y OS 45%) vs TXL + CBDCA (OR 20%, MTTP 5.1 mo, MOS 8.3 mo, 1 y OS 34%).

****H Yasuda et al (JCO 2006;24:688-94). N=120 advanced IIIB & IV. Randomized to NITROGLYCERIN patches 25 mg/d x 5 starting d-3 + NVB 25 mg/m2 d 1 & 8 + CDDP 80 mg/m2 d 1 (OR 72%, TTP 327 d, MOS 413 d) vs NVB + CDDP (OR 42%, TTP 185d, MOS 289d… What about Radiotherapy?…

R Ramblan et al (JCO 2006;24:2800-7). N=829, IIIBand IV, PS>2, only one prior ChX. Randomized to TPTC 2.3 mg/m2 d 1-5 po (1 y OS 25.1%, TTP 11.3 wk, OR 5%) vs TXT 75 mg/m2 d 1 (1 y OS 28.7%, TTP 13.1 wk, OR 5%).

********M Ando et al (JCO 2006;24:2549-56). Interstitial lung disease in Japan. Gefitinib series of 1967 patients in 84 centers. 70 cases, 31 deaths. Incidence 3.5%, mortality 1.6%, correlated with smoking, male gander and interstitial pneumonia.

R Petty et al (JCO 2006;24:1729-44). Serpin B3 elevation correlated with Platinum response in SCC (HR 0.43) and paradoxically in adenocarcinoma (HR 2.09).

Z Zheng et al (NEJM 2007;356:800-8). ICH determination of RRM1 protein (involved in nucleotide excision repair) and ERCC1 (involved in DNA excision repair complex) in N=187 operated early stage NSCLC demonstrated positivity in both genes in 30%, identified as a group with excellent prognosis and 5y OS >80%. Since ERCC1 indicate resistance to CDDP and GEM it ia difficult to explain the good prognosis but certainly indicated no need of adjuvant chemotherapy.

A Sandler et al ECOG (NEJM 2006;355:2542-50). N=878, stages IIIB & IV, no CNS, hemopthysis, low ECOG and organ disease, excluding squamous cell histology (hemorrhage). Randomized to TXL 200 mg/m2 + CBDCA AUC 6 + BV 15 mg/kg q 3 wk (MST 12.3 mo, MPFS 6.2 mo, OR 35%, Bleeding 4.4%, MOS 11.7 mo, Females 13.3%) vs TXL + CBDCA ((MST 10.3 mo, MPFS 4.5 mo, OR 15%, Bleeding 0.74%, MOS 8.7 mo, Females 13.1%).

*R Lilenbaum et al (JCO 2006;24:4825-32). N=133, second lineChX, prior Pt based Rx. Randomized to CPT 60 mg/m2 + TXT 35 mg/m2 d 1 & 8 q 3 wk + Celecoxib 400 mg bid vs CPT 100 mg/m2 + GEM 1000 mg/m2 d 1 & 8 q 3 wk. Arm with Celecoxib had decreased 1 y OS 22% vs 36%. OR<5%.

***G Giaccone et al (Clin Ca Res 2006;12:6049-55). First line Erlotinib 15o mg qd in NSCLC. N=53. OR 6/24 adenocarcinoma + 4/6 BAC + 2/8 SCC + 0/9 LCC + 0/6 other types (OR 27%), MDR 333 d. MST >1y. Compared favorably with ChX.

**D Jackman et al (JCO 2007;25:760-6). N=80. Elderly untreated patients treated with Erlotinib 150 mg qd. OR 10/ + NC 41%. MST 3.5 mo, MST 10.9 mo, 2 y OS 19%.

J Heymach et al (JCO 2007;25:4270-7). N=127 recurrent after first line Chx. Phase II: Vandetanib (inhibitor of VEGFR2 and EGFR) 100-300 mg qd + TXT 75 mg/m2 q 3wk vs TXT. PFS 17-18.7 wk vs 12 wk. Now being tested in randomized Phase III.

BC Cho et al (Cancer 2007;110:599-605). Phase I Erlotinib after Gefitinib in N=121. OR 9.5% (benefit 26.5%).

***U Gatzemeier et al (JCO 2007;25:1545-52). N=1172, phase III untreated. Randomized CDDP+GEM +/-Ermotinib vs placebo. OS HR=1.06. No diff in TTP, OR, QOL...

NSCLC: SUGERENCIAS

Cirugía:
El estadio III contiene T3N0 y T3N1 con supervivencia a 5 años 30%,y los TxN2 que son mucho peores. La cirugía radical de los N2 podria mejorar los resultados de supervivencia, ¡siempre después de quimioterapia newoadjuvante...!.

La cirugía previene fallo local!. Argumento importante porque todavía es la fuente mayor de fallos en estadios II-III.

Radioterapia:
No se dispone de datos de radioterapia split.

La radioterapia postoperatoria esta desacartada basándose en estudios antiguos y técnicas hoy obsoletas...!

La mejor radioterapia en estudios randomizados de RTOG es la continua acelerada hiperfraccionada (CHART): 1,5 Gy tid (6 h aparte) x 12 dias, con 54 Gy en 36 F.
A estos datos se podria añadir la posibilidad actual de campos conformados para poder subir la dosis total (técnicas convencionales) a 74 Gy (desde 60 Gy). Buen proyecto!.

Utilizar PCI en NSCLC para prevenir metastasis en casos de alto riesgo (estadios>II) y en respuesta completa.

Quimioradioterapia es mejor que radioterapia exclusiva!!!

TIRAPAZAMINE (sensibilizacion hipoxica) junto con CDDP aumenta la respuesta (agentes combinados OR 23%) sugestivo de sinergismo

Quimioterapia neoadjuvante:
Es el tratamiento convencional de los estadios III, con cirugía después de la quimioterapia.
La pauta antigua clásica de Gralla, confirmada por todos los autores posteriores daba a CDDP-VBL/VDS-MitoC +RT + Cirugía 60% RO, 42% reseccion, 4% pT0y 20% LTS a 3 años.
Los resultados actuales son 70% OR, 55% reseccion, 7% pT0 y 30% 3ys.
Podrían mejorarse con dos alternativas: QT-RT simultanea (CDDP-TXL) o bien con CHART (2-3x 1,5 Gy (q 6h)/d hasta 45 Gy en <3 sem... El objetivo es conseguir 80% RO, 60% reseccion, 15% pT0 y 35% 3 ys...!

Quimioterapia adjuvante:
Metanalisis demuestra aumento de supervivencia de 5% a 5 años.

Quimioterapia convencional:
La quimioterapia proporciona en metanalisis 10% aumento de supervivencia a un año en estadios IIIB-IV.

To detect a 2 mo improvement in survival in NSCLC requires > 300 pts on trial (ASCO 2000)

Agentes activos:
Los clásicos: CDDP a dosis >100mg/m2, Mito C, VBL/VDS/NVB, VP, CBDCA, IFX, Antraciclinas y 5FU. A estos se añaden los acreditados recientemente (CPT11, TOPOTECAN, GEM, TXL, TXT, EDATREXATE, MTA, CAELYX todos con 20-30% respuestas como agentes unicos).

Datos significativos: GEM es igual a CDDP+VP (OR 20%)
CDDP+ GEM o CDDP+NVB dan OR 30%
CDDP+CPT o CDDP+TXL dan OR 50% (mejor que CDDP+VP)
Resultados actuales con dos fármacos RO 35-45% y 1 y s 35-50%.
En la decada de los 90 la 2 y s ha sido uniforme <10%
Combinaciones de 3 agentes dan OR 40-70% y 1 y s >50%
El tercer agente casi siempre ha sido GEM, NVB, IFX ademas del doblete con CDDP/CBDCA y TXL/TXT.
Son prometedores CPT y Topotecan como tercer agente ademas de MTA y Edatrexate

Propuesta: TXL-CDDP-CPT11. CDDP 50 mg/m2 + CPT 120 mg/m2 + TXL 80 mg/m2 q 2 wks, con aumento de dosis de acuerdo a toxicidad...!!!

Nedaplatin (no renal toxicity) Japanese , DLT 100 mg/m2, OR 58% NSCLC (11/19)(ASCO 2000)

Inmunoterapia:
Aplicación de TIL (crecen en 80%) en estudio randomizado después de cirugía incrementa la supewrvivencia media en 10 meses en el grupo tratado (Cancer 1996;78:244-51).

IL2+LAK en estudio randomizado después de Cirugía`QT-RT proporciona aumento de supervivencia a 2 años, al doble (54%).

OK432 adj immunotherapy postop lung cancer. Metanalysis of 10 trials involving 1358 pts: Death risk 0,85 (ASCO 2000)

PANOREX Ab 17-1A, present in 66%

HMFG-1 (Mo Ab F8ab')2 against PEM -Polymorphic epithelial mucin) + EBRT… (Antisoma Res Labs St Georges' Hospital, CranmerTerrace, London, UK)

I Bolonaki et al (JCO 2007;25:2727-34). TERT 572Y (cryptic peptide)subcutaneous x 2 followed by TERT 572 native q 3 wk x 4, after ChX+RT. N=22. 12/22 completed treatment. Specific CD8+ 76%. MDR 11.2 mo. MOS 30 mo for responders and 4.1 mo for non responders.

Tratamiento de soporte:

En pacientes fragiles o de edad avanzada la pauta de NVB 30 mg/m2 d 1&8 y GEM 800-1500 mg/m2 d 1&8 (es mejor que ambos agentes unicos separadamente) proporciona 35% OR y 1 y s <50%...

ATP 75 ug/kg, q 2 sem x 7 y después q 4 sem x 3 , da beneficio en peso, fuerza y mejoria en la calidad de vida. (JNCI 2000;92:321-8).

REUNION ACINOVIC, CALVO Y BRUGAROLAS DE marzo 2001:
Estadio I : Cirugia
T1-N0-1: RT+LAK
IIB: T3-N0: QT NA + Cia + RT + LAK
IIIA: Similar
IIIB: (N2 Bulky) QTNA + QT/RT + Cia debulking en T3 Mediastino +

SCLC

Aplicaciones de biología molecular

Marcador diagnostico	c-myc (SCLC 15-44%)
Marcador diagnostico	c-myb (SCLC 87%, NSCLC 30%)
Marcador diagnostico	raf-1 (comun en SCLC & NSCLC)
Marcador diagnostico	GRP-bombesin (SCLC), proGRP (gastrin releasing hormone)
Marcador diagnostico	Chromogranin A (SCLC)
Marcador diagnostico	Rb (SCLC 90%) o del p16 (Todos SCLC presentan)
Marcador diagnostico	N-CAM , >20u/mL, + 50% SCLC (solo 34% NSE).

Marcador mal pronostico	Microvasculatura
Marcador mal pronostico	p53 mutado (enf extensa y mala respuesta a CDDP)
Marcador mal pronostico	proliferación (Ki-67, PCNA, aneuploidia, timidina)
Marcador mal pronostico	elevación citokinas (G-CSF, GM-CSF, M-CSF, IL6)
Marcador mal pronostico	microsatelitosis presente en plasma (50%). Enf residual.

Supervivencia pobre	del 3p14-23 (FHIT, target de tabaco) (SCLC 90%, Otros 30%)
Supervivencia pobre	elevación PAI-1

Supervivencia pobre LDH y Na discriminan supervivencia en SCLC-Ltd Disease

Supervivencia buena Normalizacion NSE a 4 sem (SCLC)

Significado desconocido expresión alta de FAS-ligand
Significado desconocido Telomerasa, presente en 90%
Significado desconocido bcl-2 + (50% SCLC)

Marcador de tabaquismo DRD2 (polimorfismo de dopamina reward gene)

SMALL CELL LUNG CANCER

J Y Pawel et al (JCO 2001;19:1743-9). Relapsed SCLC. Randomized to TPTC oral 2.3 mg/m2/d x 5 q 3 wk (MST 32 wk, OR 32%, Myelotoxcitiy 35.5%) and TPTC iv 1.5 mg/m2/d x 5 q 3 wk (MST 25 wk, OR 15%, Myelotoxicity 67.3%).

K Noda et al (NEJM 2001;346:85-91). M=154. Randomized to CPT 60 mg/m2 d 1, 8 & 15 + CDDP 60 mg/m2 d1 (2 yOS 19.5%, CR 2.6%, PR 84.4%) vs CDDP 80 mg/m2 d 1 + VP 100 mg/m2/d x 3 (2 y OS 5%, MST 9.4 mo, CR 9.1%, PR 67.5%). MST gain remarkable.

J Jett et al (Cancer 2003;97:2498-503). CDDP 30 mg/m2/d x 3 + VP 100 mg/m2/d x 3, cycles 1, 3 & 5; TPTC 1 mg/m2/d x 5 + TXL 200 mg/m2 d 5 + GCSF, cycles 2, 4 & 6. N=44. ED. Hematologic toxicity with ANC 70%, Plat 23%; OR 77%, MTTP 6.9 mo, MST 10.5 mo, 2 y OS 12%.

A Ardizzoni et al (JCO 2002;20:3947-55). N=244, M F up 54 mo. Randomized study comparing CPA 1 g/m2 + DOX 45 mg/m2 + VP 100 mg/m2 x 3 q 3 wk (Hemotol toxicity grade IV 50%, OR 79%, MST 54 wk, 2 y OS 15%) vs **higher dose** CPA 1250 mg/m2 + DOX 55 mg/m2 + VP 125mg/m2 x 3 + GCSF repeated q 2 wk (Hematol tox 79%, OR 84%, MST 52 wk, 2 y OS 18%). DI doubled sine benefit.

A Ardizzoni et al (Clin Ca Res 2003;9:143-50). N=110 resistant. CDDP 60 mg/m2 + TPTC 0.75 mg/m2/d x 5 q 3 wk. Hematologic toxicity ANC 50-62%, Plat 44-54%. OR 30%, MST 6.4 mo.

M Reck et al (JNCI 2003;95:1118-27). N=614, stage IV. Randomized to TXL 175 mg/m2 + VP 125-100 mg/m2 x 3 + CBDCA AUC 5 q 3 wk (OR 72.1%, MST 12.7mo, 2 y OS 17%, 3 y OS 17%) vs VCR 2 mg + VP 125-160 mg/m2 x 3 + CBDCA AUC 5 (OR 69.4%, MST 11.7, 2 y OS 16%, 3 y OS 9%).

*******R Kowaki et al MDACC (Sem Oncol 2003;30:56-70. Review. Work up: Cognitive evaluation done at diagnosis demonstrate 83% LD patients have deficiencies. When LDH is elevated BM aspiration biopsy should be carried out. Thoracocentesis when pleural effusion is present. PET. Prognostic factors are: age and gender, stage, continuing smoking, LDH, Na, Phosphatase alkaline. ChX: CAV-PE-IFX/TXL addition; CPT+CDDP>PE; Higher dose >lower dose (Arriagada, NEJM 1993; 329:

1848-52, indicating CDDP 100/CPA 300/DOX 40/VP 75 is better than CDDP 80/CPA225/DOX40/VP75 with a 2 y DFS 28% vs 8%; and Hainsworth, JCO 1997; 15; 3464-70), indicating that TXL 200/PE/RT is better than TXL 135/rest equal with CR 71% vs 40%. Combined ChX + RT increase 2 y OS from 10-15% to 25-30%, with still intrathoracic recurrences. Local control improves 25% & 2 y OS 5.4%. Also early thoracic irradiation with bid fractionation (1.5 Gy), 45 GY in the thorax improve local control from 40% to 55% and 2 y OS from 20% to 45%. Future improvements in dose elevation up to 65 Gy, and volume of thoracic irradiation in the postchemotherapy volume.

******D Fried et al (JCO 2004;22:4785-93). Randomized trials timing thoracic RT in LD: Benefit for early RT (RR 1.17 2 y OS and RR1.13 3 y OS); Benefit for hyperfractionation (RR 1.44 2 y OS and 1.39 for 3y OS); No differences for once or twice daily fractionation; Benefit for CDDP based ChX (no diff for non CDDP based ChX) (RR 1.3 2 y OS, RR 1.35 3 y OS).

C Rudin et al (JCO 2004;22:1110-7). G3139, Oblimerson sodium (bcl2 antisense oligonucleotide). N=16. Oblimersen Na 5 mg/kg/d (escalated to 7 mg/kg)from d1-8 q 3 wk +CBDCA AUC 6 on d6 + VP 80 mg/m2 d 6-8. OR 12/16 (86%), NC 2/16. MTTP 5.9 mo.

JY Han et al (JCO 2005;23:3488-94). N=35 LD. CPT 80 mg/m2 + CDDP 40 mg/m2 wkly x 3 q 4 x 2 induction, then RT bid 45 Gy + concurrent CDP 60 mg/m2 + VP 100 mg/M2/d x 3 x 2 cycles. OR 97% after induction and 100% after RT. MF up 26.5 mo, MOS 25 mo, 2 y OS 54%, MPFS 12.9 mo, 2 y PFS 36.1%.

M Socinski et al (Sem Oncol 2005;32:1-4). First line randomization. CDDP 75 mg/m2 + Alimta 500 mg/m2 q 3 wk (N=35, OR76%) vs CBDCA AUC 5 + Aslimta (N=33, OR 58%).

**H Bozcuk et al (Cancer 2005;104:2650-7). Meta-analysis of maintenance ChX (14 trials, 2.550 patients), indicated improvement in 1 y OS 9% and 2 y OS 1%.

A Brau & I Tannock (JCO 2006;24:1020-2). Meta-analysis of early vs late RT showed a 1.8% decrease in OS per week delay over 3wk after the start of ChX. Hypothesis is repopulation resistance.

JR Eckardt et al (JCO 2006;24:2044-51). N=784, ED. Randomized to TPTC 1.7 mg/m2 qd x 5 + CDDP 60 mg/m2 d 5 q 3 wk(OS 39.3 wk, 1 y OS 31%, OR 63%, TTP 124.1 wk) vs VP 100 mg/m2 qd x 3 + CDDP 80mg/ m2 d 1 (OS 40.3 wk, 1 y OS 31%, OR 69%, TTP 25.1 wk. Similar results.

S Onoda et al (JCO 2006;24:5441-7). N=60, refractory. Amrubicin 40 mg/M2 qd x 3 q 3 wk. OR 50%, PFS 2.6 mo, OS 11.6 mo. Active.

DH Lee et al (Clin Ca Res 2007;13:6182-6). Phase I, ED untreated. Belotecan 0.5 mg/m2/d 1-4 + CDDP 60 mg/m2 d 1 q 3wk. OR 13/17 (76.5%).

SJ Antonia et al (Clin Ca Res 2006;12:878-87). N=29. Patients with progression after conventional ChX treated with DC transfected with adenovirus carrying wild type p53,

and 57% presentred p53-T cell specific response without response: OR 1 PR + 7 NC + 21 PD. Subsequent chemotherapy on 23 patinets showed 3 CR + 10 PR + 4 NC (third line), MOS 11.8 mo. It appears that specific vaccination improved second line ChX response.

SE Child et al (JCO 2007;25:3124-9). Phase II N=76. PE x 6 cycles + bid TRT on cycles 4 & 5 concurrent 30 Gy/20 bid F & 2 wk break x 2 + PCI at 3rd cycle (250 Gy/10F). Hemat tox grade >3= 95%, 2% CNS failure. 5 yOS 24% and MST 20 mo, 5y in filed recurrence 34%.

JH Sohn et al. (Cancer 2007;109:1845-50). Phase II study N=33. CPT 60 mg/m2 d 1, 8, % 15 + CDDP 40 mg/m2 d 1 & 8 q 4 wk x 6 + TRT 1.8 Gy/d from 2nd cycle up to 45-54 Gy + PCI 30 Gy /10F in patients with a CR. Results: OR 87.9%, CR 45.5%; MPFS 14.4 mo, MOS 26.1 mo; 2 y PFS 26.8% and 2 yOS 54.9%.

B Slotman et al (NEJM 2007;357:664-72). PCI in ED. Randomized study N=286. PCI prevented metastases HR=0.27. 1 y cumulative mets 14.6% vs 40.4%.

SCLC: SUGERENCIAS

Radioterapia:
PCI: RR =,35 incidencia de mets SNC, beneficio de supervivencia 5-7% (RR 0,85)

RT-TI lo mas precoz posibkle, no up-front sino en consolidación.

Quimioterapia convencional:

CAV es igual a PE en OR y supervivencia y exhiben resistencia cruzada.

CODE (High DI) similar a CAV/PEV alternante!

ICE: IFX 5 g/m2 + CBDCA 300 mg/m2 + VP 120 mg/m2/d x 4 da resultados similares.

Pauta MDACC: CDDP 20 mg/m2/ x 3 + VP 40 mg/m2 po d 1-14 + IFX 1200 mg/m2/d x 3 + Accel RT 1,5 Gy bid x 30 (45 Gy) d 1-19, cycle 1. PCI 25 Gy dsespues de RC. Los resultados son RC 67%, OR 78%, MST 23 mo, 3 ys 39%, 2 ys 50%.

K Antmann (DFCI): Consolidacion con ABMT (CPA+BCNU+CDDP), con OR 100%, CR 50%, 2 ys 53% y 5 ys 41%.

Nuevos agentes activos: CPT 47% OR
TOPOTECAN 40% OR
TXL 30% OR
GEM 25% OR
NVB
ALIMTA
CDDP+CPT es mejor que CDDP+VP en OR y en supervivencia

TPT+CDDP >VP+CDDP in extensive SCLC: OR 89% vs 67%, MST 420 d vs 300, & 1ys 60% vs 40% (ASCO 2000, 1887)
CPT 50 mg/m2 d 1, 8 &15 + CDDP 100 mg/m2 + RT thorax: OR 93.8% in SCLC limited dx (ASCO 2000, 1999)
ESMO 25th, Hamburg, Oct 2000: VP, 120 mg/m2 d 1-3, AUC >254,8 associated with better survival (1 ys 43% vs 0%; MST 11.3 mo vs 5.3 mo)

Pauta CUN UK alt CAF-VCR y PE-VCR con TI+ PCI al 3 cycle. OR 83%, MST 33 mo, 2ys 65%, 10 y s 50% (actuarial**)** (mejores resultados de la literatura). Deberia aplicarse el concepto de AML de inducción-consolidacion-reinduccion y mantenimiento. De acuerdo con el mismo nos falta la reinducción ya que los otros aspectos estan reflejados en nuestra pauta actual.
Propuesta: Llevar a primera linea CPT-11 o TOPOTECAN!!! REUNION Marzo 2001 (Acino, Calvo, Brugarolas): Mantener 6 alt + RT sin modificaciones, seguir con CPT 150 mg/m2 + GEM 2000 mg/m2 q 2 wks x 6 despues de la RT en estadio limitado!!!

Moduladores biológicos:

CARBIDOPA (Sinemet 25/100, 6-8 cp/dia). Letala SCLC a traves de metabolismo de 5HT (no por apoptosis). Se combina bien in vitro con QT (Topotecan o VP) Clin Ca Res 2000;6:4365-72).

Inmunoterapia:
IL2 en PBL: >1550 pg/mL o menos de este nivel se correlaciona con supervivencia, 2 y s 50% vs 15% (Ann Oncol 1997;8:457-61).

Los pacientes que presentan AntiHu tienen mejor pronostico de respuesta y supervivencia.

Late relapses son 15%, segundos tumores 20%.

Tratamiento de soporte:
Secrec inadec ADH: Demeclociclina (Varibiotic, 150-300 mg/q 6-8 h, resuelve en < 3 sem (Induce diabetes insípida en tubulo distal con refractariedad a vasopresina).
Cushing: Ketokonazole 200 mg/tid inhibe síntesis de esteroides
Lambert-Eaton: Guanetidina
Ab mediated HU protein (AntiHu 15%).

Anticuerpos monoclonales:

N901	MoAb N-CAM-RICIN, 20 ug/kg/d x 7, civi (trials 2000)
MoAb BEC-2	Contra GD3. Estudio randomizado Observ vs BEC2+BCG >600 pts iniciado en 1998.