

Participació de l'ICO al Congrés ECCO

Especialistes de diferents serveis dels tres centres de l'ICO participen en l'European Cancer Conference (ECCO) que comença el proper dilluns 25 de setembre a Barcelona.

A més, la Societat Europea d'Oncologia Mèdica ha acreditat l'ICO com un centre oncològic d'excel·lència per a les cures pal·liatives. La cerimònia oficial serà dimarts 25 a les 09:00 en el marc del congrés

Us oferim un breu resum de l'activitat de l'ICO a l'ECCO:

Infermeria

-**Paz Fernández**, de Recerca en Infermeria, és membre del comitè executiu científic del congrés i modera dues taules. Organitza un simposi paral·lel sobre mama.

-**Esther Corrales**, de l'ASPI, coordina el taller Com evaluar els indicadors sensibles de la pràctica de la infermeria en càncer

-**Marisa Martínez**, infermera UIC, coordina taller sobre noves teràpies

Es presenten dos pòsters: un de l'ICO Girona i l'altre de l'Hospital de Dia de l'ICO Hospitalet. A més, un equip d'infermeres d'arreu del món visita l'ICO dilluns 24 de setembre.

Psico-oncologia (Hospitalet)

Francisco Gil es moderador de la taula Psychosocial care across the cancer continuum

Oncologia Mèdica (Girona)

Teresa Puig Miquel, del Grup Metabolisme i Oncogens de l'ICO Girona presenta un pòster i una comunicació oral.

Oncologia Radioteràpica (Hospitalet)

Ferran Guedea presenta la proposta Europea Pacarad (Patterns of Care and model of Radiotherapy services contributing to improvement in quality, accessibility and equity in health care). 26 de setembre.

Oncologia mèdica (Badalona)

Rafael Rosell és membre del Comitè organitzador nacional. A més participa en dues rodes de premsa, una dilluns 23 i una dimarts 24 sobre el paper del gen BRCA1 en la resposta al tractament en càncer de pulmó.

El seu equip, a través del Grup Espanyol de Càncer de Pulmó, participa en diferents comunicacions orals i pòsters.

A continuació us oferim els abstracts de les comunicacions que es presenten.

Differential inhibitory effects of epigallocatechin-3-gallate (EGCG) and C75 in cancer fatty acid metabolism

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Purpose: Endogenous fatty acid metabolism is crucial to maintain the cancer cell malignant phenotype. Lipogenesis is regulated by the enzyme fatty acid synthase (FASN); and fatty acid oxidation pathway is regulated by carnitine palmitoyltransferase-1 (CPT-1). Inhibition of FASN has been shown to induce apoptosis in a variety of cancer cells, and consequently to be a potential therapeutic target for the treatment of cancer. To date, only a few inhibitors of FASN have been reported (cerulenin, C75, EGCG, orlistat, triclosan), although the degree of specificity of this inhibition has not been addressed.

Experimental design: We have evaluated the effects of C75 and (-)-epigallocatechin-3-gallate (EGCG) on fatty acid metabolism pathways (FASN and CPT-1 activities), cellular proliferation, induction of apoptosis and cell signalling (HER2, ERK1/2 and AKT cascades) in breast cancer cells and the effect of reduced FASN activity on adipocyte differentiation of 3T3-L1 cells.

Results: C75 and EGCG had comparable effects in blocking FASN activity. Treating cancer cells with C75 or EGCG induced apoptosis and caused a decrease in the active forms of oncoprotein HER2, AKT and ERK1/2 to a similar degree. In addition, C75 and EGCG reduced dramatically visible lipid droplet accumulation during preadypocyte differentiation. We observed, in contrast, marked differential effects between C75 and EGCG on fatty acid oxidation pathway. While EGCG had either no effect or a moderate reduction in CPT-1 activity, C75 stimulated CPT-1 activity (up to 129 %), even in presence of inhibitory levels of malonyl-CoA, a potent inhibitor of the CPT-1 enzyme.

Conclusions: In cancer cells, pharmacological inhibition of FASN occurs uncoupled from the stimulation of CPT-1 with EGCG but not with C75, suggesting that EGCG might be free of the CPT-1 related in vivo weight-loss that has been associated with C75. Our results establish EGCG as a potent and specific natural inhibitor of fatty acid synthesis (FASN), which may hold promise as a target-directed anticancer drug.

Individualized chemotherapy based on methylation of serum or plasma DNA

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Non-invasive tests for customizing chemotherapy could be performed based on the analysis of extracellular DNA circulating (cirDNA) in the blood. Numerous studies have demonstrated tumor-specific alterations, such as aberrant promoter hypermethylation, in cirDNA recovered from serum or plasma of non-small-cell lung cancer (NSCLC) patients and the absence of methylated DNA in healthy subjects (Ramirez et al. *Cancer Lett* 2003). For translational research studies in NSCLC, cirDNA is an abundant source of material that could be examined by methylation-specific PCR (MSP). Several layers of evidence indicate that several methylated genes in cirDNA could be potential predictive markers. Methylation of the mitotic checkpoint gene CHFR could indicate sensitivity to microtubule inhibitors, and we have shown that methylation of DNA repair genes, such as O⁶-methyl-guanine-DNA methyltransferase, in cirDNA indicates sensitivity to 1,3bis(2-chloroethyl)-1-nitrosourea (Balaña et al. *Clin Cancer Res* 2003). In addition, 14-3-3 σ , FANCF and BRCA1 methylation indicates sensitivity to cisplatin. Other genes, such as Werner, belonging to the RecQ family of helicases can indicate sensitivity to irinotecan. However, in NSCLC, BRCA1 methylation is not commonly seen, FANCF1 methylation is low, and Werner methylation has not been confirmed in our experience. We have also examined other crucial mitotic spindle checkpoint genes, such as BubR1, which is not methylated.

We have concentrated our translational research in CHFR and 14-3-3 σ , since both are methylated in cirDNA in more than 30% of NSCLCs. The CHFR gene molecularly defines the existence of a checkpoint that regulates entry into metaphase. The CHFR protein contains a central ring finger domain that has ubiquitin ligase activity. CHFR directly ubiquitinates PIK1, Aurora-A and possibly other substrates, since it contains residues homologous to those of c-Cbl. We have observed that unmethylated CHFR in cirDNA confers greater sensitivity to second-line EGFR tyrosine kinase inhibitors (TKIs) in NSCLCs, both with and without EGFR mutations. The 14-3-3 proteins regulate cell survival and programmed cell death. We have found that in stage IV NSCLC patients treated with gemcitabine/cisplatin, median survival was longer in the cirDNA 14-3-3 σ methylation-positive group (15 vs 10 months; P=0.004) (Ramirez et al. *J Clin Oncol* 2005). A customized trial is planned for stage IV NSCLC patients, in which those with methylated 14-3-3 σ in cirDNA will receive gemcitabine/cisplatin, and those with unmethylated 14-3-3 σ will receive vinorelbine/cisplatin. One hundred and forty patients per arm are required to test that there are no differences in progression-free survival.

A prognostic model based on BRCA1 mRNA expression: A new determinant of outcome in early non-small-cell lung cancer (NSCLC)

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Background: Following surgical resection in operable NSCLC, 5-year survival is 60% in stage I, 39% in stage IIB and 23% in stage IIIA, with relapse commonly as distant metastases. The average benefit of adjuvant chemotherapy is 5%, ranging from nil in stage I to 15% in stage II-III A. Caretaker genes involved in keeping genetic alterations to a minimum include the nucleotide excision repair genes ERCC1 and myeloid zinc finger 1 (MZF1), which mediates ERCC1 expression, and other stability genes, such as BRCA1, which control processes involving large portions of chromosomes. Thioredoxin-1 (TRX1) is a redox protein overexpressed in NSCLC that is correlated with poor prognosis, and TWIST contributes to metastasis by promoting epithelial-mesenchymal transition. **Methods:** In order to identify p with a high risk of relapse, we investigated the expression of these 5 transcripts in frozen resected tumors from 126 resected NSCLC p by real-time quantitative PCR. Gene expression was normalized using β -actin and 18SrRNA expression as internal references. **Results:** Adenocarcinoma (adeno), 33 p; squamous cell carcinoma (SCC), 93 p. Stage: IA, 18 p; IB, 53 p; IIB, 33 p; IIIA, 22 p. Tumoral transcript expression with β -actin: ERCC1, 1.23; MZF1, 0.53; BRCA1, 3.65; TRX1, 1.82; TWIST, 7.75. A strong correlation was observed between the expression of ERCC1, MZF1 and BRCA1 ($P < 0.001$). Expression of each of the 5 transcripts was higher in SCC than in adeno ($P < 0.001$). Median survival (MS): low ERCC1 (< 1.5) = not reached (NR), high ERCC1 = 33 months (m) ($P = 0.21$); low MZF1 (< 0.5) = NR, high MZF1 = 33 m ($P = 0.04$); low BRCA1 (< 5) = NR, high BRCA1 = 22 months (m) ($P = 0.01$); low TRX1 (< 0.8) = NR, high TRX1 = 39.5 m ($P = 0.02$); no differences in MS according to levels of TWIST. In a multivariate Cox model for survival, BRCA1 and stage emerged as independent prognostic variables (Table). The prognostic value of BRCA1 has been validated in a separate set of 58 NSCLC p.

Conclusion: Increased BRCA1 is associated with shorter survival, and BRCA1 assessment could be useful for customizing adjuvant chemotherapy.

	HR	95% CI	P
Stage			
IA-IB	1		
IIA-III A	1.75	1.02-3.06	0.04
BRCA1 levels			
≤ 5	1		
> 5	1.77	1.02-3.06	0.04

XPD 312 single nucleotide polymorphism (SNP) predicts survival in stage IIIA-B non-small-cell lung cancer (NSCLC) patients (p) <59 years (y) treated with chemotherapy followed by surgery

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Background: SNPs in DNA repair genes may affect response to cytotoxic therapy. We investigated SNPs in XPD codons 751 and 312 and in RRM1 -37 in 109 stage IIIA (N2) and IIIB NSCLC p treated with neoadjuvant chemotherapy and correlated results with event-free (EFS) and median (MS) survival. **Methods:** p eligible for surgery received cisplatin day (d) 1, gemcitabine d 1,8, docetaxel d 1,8,15, every 3 weeks for 3 cycles, followed by thoracotomy. DNA was extracted from baseline peripheral lymphocytes and genotyping was performed by Taqman. **Results:** Median age, 60 y (range 31-77); 92 males (84%); 45 squamous cell (41%). 4 p (3.9%) attained complete response; 55 (53.9%) partial response. 75 p underwent surgery (62 complete, 13 incomplete resection); remaining 34 p were unresectable. Median follow-up was 15.7 months (m) (range, 0.5-74). MS for p still alive is 49.8 m (range, 6.7-74). MS: 48 m with complete resection, 13 m with incomplete resection, 17 m for unresected p. In the univariate analysis of survival, age <59 y (P=0.03), resection (P<0.001) and XPD312 AspAsp (P=0.05) emerged as predictive markers of longer survival. For all 109 p, those with XPD312 AspAsp had longer EFS and MS than p with Asn variants (Table). In addition, for 51 p <59 y, EFS was longer for 24 p with XPD312 AspAsp (36.4 m) than for 27 p with Asn variants (9.8 m) (P=0.009); MS in this group of younger p was 45.4 m for AspAsp vs 15.8 m for Asn (P=0.04). No other significant correlation between SNPs and survival was observed (Table). **Conclusions:** Interaction between SNPs, age and risk of lung cancer has previously been described. XPD312 AspAsp in p <59 y predicts longer survival in stage IIIA (N2) and IIIB NSCLC treated with neoadjuvant chemotherapy.

	EFS			MS		
	N	m (95% CI)	p	N	m (95% CI)	p
XPD751						
LysLys	45	13.22 (3.49-22.95)	0.13	45	32.14 (5.08-59.20)	0.15
LysGln & GlnGln	64	8.82 (6.11-11.52)		64	14.90 (10.39-19.41)	
XPD312						
AspAsp	55	13.98 (4.79-23.17)	0.03	55	32.14 (7.58-56.70)	0.05
Asp & AsnAsn	54	7.34 (4.53-10.14)		54	12.04 (6.09-17.99)	
RRM1-37						
CC	59	9.11 (6.03-12.19)	0.87	59	14.97 (4.61-25.32)	0.53
CA & AA	49	10.79 (8.22-13.36)		49	16.84 (1.50-32.18)	

Elevated levels of thioredoxin (Trx) in serum correlate with poor outcome in docetaxel (doc)/cisplatin (cis)-treated stage IV non-small-cell lung cancer (NSCLC) patients (p)

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Background: Chemotherapy causes the production of reactive oxygen species (ROS), which facilitates cancer cell death. Trx protein functions as a ROS scavenger and a negative regulator of apoptosis signal regulating kinase-1 (ASK-1). High levels of Trx are associated with chemoresistance. 14-3-3 σ proteins are involved in cell cycle control and protein trafficking. Methods: Trx ELISA and 14-3-3 σ methylation-specific PCR were performed in baseline serum from 107 stage IV NSCLC p treated with doc/cis. Results: Median age, 60 (range, 32-79); male, 87 (81.3%). PS: 0, 27 (25.2%); 1, 80 (74.8%). Adenocarcinoma, 46 (43.8%); squamous cell carcinoma, 40 (38.1%); 21 p had large cell or unspecified histology. Complete response, 1 p; partial response, 20 p; overall response rate, 20%. Median Trx level, 97.4 (range, 18.8-763.1). Serum was available for 14-3-3 σ methylation analysis in only 88 p. 14-3-3 σ was methylated in 43 p (48.9%). A significant correlation was observed between 14-3-3 σ methylation status and Trx levels (Table). 4 p with methylated and 17 with unmethylated 14-3-3 σ had Trx levels >182.8 (P=0.003). Median Trx levels were 103.5 in responders and 94.3 in non-responders (P=0.96). Time to progression (TTP) was 5.6 months (m) for 27 p with Trx <49.6, 4.4 m for 53 p with Trx 49.6-182.8, and 3.8 m for 27 p with Trx >182.8 (P=0.02). In a Cox multivariate analysis, Trx levels emerged as an independent variable for TTP when 14-3-3 σ was included in the model. Hazard ratios: 1.3 for PS1 (P=0.84); 1.05 for 14-3-3 σ unmethylated (P=0.22); 1.4 for Trx 49.6-182.8 and 1.95 for Trx >182.8 (P=0.04). Conclusions: Serum Trx levels can predict TTP in doc/cis-treated p. The additional role of 14-3-3 σ methylation may be more clearly demonstrated in cis/gemcitabine regimens.

Trx Levels			
14-3-3 σ	≤ 49.7	49.7 - 182.8	> 182.8
methylated	11 (25.6%) (47.8%)	28 (65.1%) (63.6%)	4 (9.3%) (19%)
unmethylated	12 (26.7%) (52.2%)	16 (35.6%) (36.4%)	17 (37.8%) (81%)

Gene expression levels of ribonucleotide reductase subunit M1 (RRM1), tyrosyl-DNA phosphodiesterase (Tdp1), nuclear factor of activated T cells (NFAT) and BubR1 mRNA expression in completely resected chemo-naïve non-small-cell lung cancer (NSCLC) patients (p)

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Background: A relationship between gene transcripts and survival in operable NSCLC is now emerging. RRM1 is involved in DNA repair, Tdp1 is implicated in the repair of CPT-induced topoisomerase damage, and NFAT promotes cancer invasion. BubR1 is a key spindle checkpoint gene, and altered BubR1 mRNA levels are associated with lymph node metastasis and chromosome instability. **Methods:** In order to identify p with a high risk of relapse, we examined the expression of these four genes in frozen resected tumors from 126 resected NSCLC p by real-time quantitative PCR. Gene expression was normalized using β -actin expression as internal reference. **Results:** Adenocarcinoma (adeno), 33 p; squamous cell carcinoma (SCC), 93 p. Stage: IA, 18 p; IB, 53 p; IIB, 33 p; IIIA, 22 p. Tumor transcript expression: RRM1, 2.10; Tdp1, 1.77; NFAT, 0.56; BubR1, 16.40. Expression of RRM1, Tdp1 and BubR1 was higher in SCC than in adeno ($P < 0.001$). Median time to relapse (TTR) was longer for p with low levels of RRM1 ($P = 0.11$), Tdp1 ($P = 0.86$), NFAT ($P = 0.29$), or BubR1 ($P = 0.44$) (Table). A significant trend towards longer survival was also observed in stage I p with low RRM1 ($P = 0.06$). In a multivariate Cox model, tumor size > 4 cm and stage III predicted shorter TTR and survival. **Conclusion:** Increased mRNA expression of these genes is associated with shorter TTR; this knowledge could be useful for customizing adjuvant chemotherapy.

	N	Median TTR	95% CI	P
RRM1				0.11
≤ 1.65	61	NR	-	
> 1.65	60	25 m	14.4-35.6	
Tdp1				0.86
≤ 1.57	60	NR	-	
> 1.57	61	35 m	-	
NFAT				0.29
≤ 0.46	61	NR	-	
> 0.46	61	35 m	18.4-51.5	
BubR1				0.44
≤ 12.28	61	NR	-	
> 12.28	61	31 m	-	

14-3-3 σ and checkpoint with forkhead and ring finger (CHFR) methylation in serum in erlotinib-treated non-small-cell lung cancer (NSCLC) patients (p) with EGFR mutations

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Background: 14-3-3 proteins have 130 potential binding partners, including Cbl. 14-3-3 expression can prevent mutant EGFR binding to Cbl, impairing ubiquitination and endocytosis. 14-3-3 σ is frequently methylated in NSCLC; we hypothesized that in the presence of EGFR mutations, methylated 14-3-3 σ could permit the formation of the EGFR-Cbl complex. CHFR is a checkpoint that delays entry into metaphase in response to mitotic stress. Methods: 73 stage IV NSCLC p with EGFR exon 19 deletion or exon 21 L858R mutation received first- or second-line erlotinib single therapy. 14-3-3 σ and CHFR methylation was examined in the baseline serum of these p. Results: Median age, 63 (range, 26-83); females, 48 p (65.8%); Caucasian, 72 p, Asian, 1 p; never-smokers, 45 p, ex-smokers, 21 p, smokers, 7 p; adenocarcinoma, 64 p, large cell carcinoma, 9. PS: 0, 19 p, 1, 42 p, 2-3, 12 p. 14-3-3 σ was methylated in 39.7% and CHFR in 42.5% of p. No differences in p characteristics were observed according to methylation status. Complete response was observed in 11.1% of p, and partial response in 75.4%. Overall response was 86.5%. There was a trend toward a higher response rate in p with unmethylated CHFR (94.4% vs 76.6%; P=ns). Overall median time to progression (TTP) and survival (MS) have not been reached either in first- or second-line. However, when split according to methylation status, there was a trend toward better TTP and MS in both first- and second-line in p with methylated 14-3-3 σ . TTP in second-line in p with methylated 14-3-3 σ has not been reached, while it was 10.8 months (m) for p with unmethylated 14-3-3 σ (P=ns). TTP in second-line in p with methylated CHFR was 5.2 m but was not reached for p with unmethylated CHFR (P=0.05). Conclusions: Methylated 14-3-3 σ can permit Cbl binding to mutant EGFR and predict longer-lasting response to erlotinib in p with EGFR mutations. The precise role of CHFR warrants further research. Complete data will be presented.

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High correspondence between EGFR mutations in tissue and in circulating DNA form non-small-cell lung cancer (NSCLC) patients (p) with poor performance status (PS)

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Background: We evaluated the correspondence between EGFR mutations in NSCLC tissue and matched serum DNA and the value of EGFR mutations as a serological marker. **Methods:** 121 Spanish stage IV NSCLC p received customized first- or second-line erlotinib monotherapy based on the presence of EGFR mutations in the tumor tissue. Serum genomic DNA was obtained from all p prior to erlotinib administration. EGFR exon 19 deletions were studied by length analysis of fluorescently labeled PCR products and the exon 21 L858R mutation by a PCR Taqman assay.

Results: The EGFR mutation status in the serum was consistent with that in the tumor tissue of 82/121 p (68%) and of 15/16 p (93.8%) with PS 2 had mutations. Overall, 64.3% of p had an exon 19 deletion and 35.7% had L858R. 78% of mutations were found in females ($P=0.01$) and 77.6% in never-smokers ($P=0.07$). Response rate was 88% in p with mutations only in the tumor and 87% in p with mutations in tumor and serum. Complete responses were observed in 20% of p with mutations in tumor and serum vs 4% of p with mutations only in tumor ($P=0.09$). With a median follow-up of 6.8 months (m) (range, 1.2-17.6), time to progression (TTP) and median survival have not been reached. A trend to better outcome was seen in p without serum EGFR mutations. TTP was longer for p with EGFR exon 19 deletions (not reached) than for p with L858R (7.7 m) ($P=0.02$). TTP for p with PS 2 with exon 19 deletions was not reached, while it was 2.7 m for p with L858R ($P=0.17$). **Conclusions:** EGFR mutations in serum could be a non-invasive source of information on the genotype of the original tumor cells and could be a useful tool to predict p response to erlotinib, especially in p with poor PS.

Role of ERCC1, XRCC3, Aurora A and TGFBR1 gene single nucleotide polymorphisms (SNP) and CHFR and 14-3-3 σ methylation in a customized cisplatin (cis) trial based on ERCC1 mRNA levels in stage IV non-small-cell lung cancer (NSCLC) patients (p)

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Background: The primary aim of this trial was response. In both the control arm and the genotypic arm with low tumor ERCC1 mRNA levels, p received docetaxel(doc)/cis while in the genotypic arm with high tumor ERCC1 mRNA levels, p received doc/gemcitabine. Response was significantly higher in the genotypic arms. We examined 324 p for genetic markers that could influence response, including ERCC1 118 C/T, ERCC1 C8092A, XRCC3 241 (Thr to Met), Aurora A 91 T>A, Aurora A 169G>A, a SNP within intron 7 of the TGFBR1 gene (Int7G24A), and an in-frame germline deletion (TGFBR1*6A). Methylation of 14-3-3 σ and CHFR were also analyzed. **Methods:** DNA from peripheral lymphocytes was used for genotyping (Taqman assay) and methylation-specific PCR was used for 14-3-3 σ and CHFR in pretreatment serum DNA. **Results:** There were no differences between clinical characteristics and the different SNP types, except that Aurora A 91 AA type had higher tumor ERCC1 mRNA levels (P=0.005). No relationship was found between ERCC1 SNPs and tumor ERCC1 mRNA levels. A strong correlation was found between the Int7G24A and XRCC3 241 SNPs (P=0.03). The Int7G24A GA type had a higher odds ratio (OR) of response (OR 2.32, P=0.02); the OR for the AA type was 3.15. XRCC3 241 MetMet had lower probability of response (OR 0.23, P=0.04). Neither other SNPs nor methylation influenced response. The best multivariate model for response was observed in p with PS 0, low ERCC1 levels, and XRCC3 241 SNP (Table). **Conclusions:** Further research is warranted to define the role of the TGFBR1 Int7G24A gene in customized treatments.

	N	OR (95% CI)	P
ARM			
Control	126	0.57 (0.34-0.93)	0.02
Low ERCC1	114	1 ref	
High ERCC1	84	0.80 (0.46-1.39)	0.54
ECOG PS			
0	124	1 ref	
1	200	0.55 (0.35-0.85)	0.004
XRCC3			
ThrThr	138	0.82 (0.51-1.32)	0.42
ThrMet	155	1 ref	
MetMEt	31	0.30 (0.12-0.72)	0.007

Vinorelbine (VRL) plus gemcitabine (GEM) as first-line treatment for elderly patients with advanced non-small-cell lung cancer (NSCLC): Molecular correlates

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Background: The clinical benefit of non-cisplatin doublets vs single-agent therapy in elderly or unfit p is still controversial. The present study focuses on the clinical outcome of VRL/GEM in elderly p and the role of functional status and comorbidities. Predictive genetic markers of response to VRL/GEM will also be examined in genomic and cDNA from tumor and circulating tumor DNA.

Materials: 145 chemo-naïve p with stage IIIB (pleural effusion or supraclavicular lymph nodes)-IV or recurrent NSCLC and age > 70 years were accrued at 32 sites between April 2004 and January 2006. Treatment consisted of VRL 25 mg/m² IV or 60-80 mg/m² oral plus GEM 1200 mg/m², days 1, 8 every 21 days. Activities of daily living (ADL), instrumental activities of daily living (IADL) and comorbidities were evaluated. DNA samples were collected from primary tumors for the assessment of microtubule associated protein 4 (MAP4) and from serum for checkpoint with forkhead-associated and ring finger (CHFR) methylation.

Results: Data on 130 p is available for toxicity and 95 for response. Median age 76 years (69-83); males: 86.8%; smokers: 70.5%; PS 0-1: 83.9%; adenocarcinoma: 34.4% / squamous: 48%; stage IIIB: 22.7%, IV: 77.3%. Self-sufficiency in ADL and IADL was 77.4% and 45.2% of the p analyzed. 68% of the p had comorbidities. Median cycles: 3 (1-8). 461 cycles (cy) were performed, 16.3% were delayed and 2.1% had dose reduction. Hematological toxicities: neutropenia grade 3-4, 12.5% p (4.1% cy); thrombocytopenia grade 3-4, 3.1% p (1.3% cy); grade 3 anemia, 3.1% p (0.9% cy). Efficacy in evaluable population: PR, 23.2% (95% CI, 15.1% to 32.9%); SD, 41.1%. 24 p died during the treatment period (non toxicity related) and 21 p were not evaluable. With a median follow-up of 5.8 months, median survival for the whole population was 4.97 months (m), progression free survival 4.53 m, event free survival 3.43 m, 1-year survival 26.6%. Statistically significant differences in median survival were observed among subgroups: PS 0-1/2, 6.5 m vs. 2.3 m (p<0.001); sex male/female, 4.5 vs. 9.7 m (p 0.027); ADL <6/=6, 3.4 vs. 7.1 m (p 0.023).

Conclusions: The combination of VRL and GEM is effective, presenting a favourable response/toxicity ratio in elderly p with advanced NSCLC. A genomic analysis is ongoing.

Co-authors:

Cisplatin (CDDP) plus vinorelbine (VRB) as first-line treatment for patients with advanced non-small-cell lung cancer (NSCLC): Molecular correlates

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Background: The combination of cisplatin plus vinorelbine is a commonly used regimen for first-line therapy in advanced NSCLC. The correlation between predictive genetic markers and clinical endpoints may improve the prediction of treatment success and thereby the tailoring of chemotherapy. In this trial, predictive genetic markers of response to CDDP/VRB were examined in genomic DNA and cDNA derived from tumors and circulating tumors.

Materials: From April 2004 to January 2006, 238 chemotherapy-naïve patients with stage IIIB (pleural effusion or supraclavicular lymph nodes)-IV or recurrent NSCLC were accrued at 35 sites. Treatment consisted of CDDP 75 mg/m² IV day 1 plus VRB 25 mg/m² IV or 60-80 mg/m² oral, days 1, 8 every 21 days. DNA samples were collected from primary tumors for the assessment of microtubule associated protein 4 (MAP4) and from serum for the checkpoint forkhead-associated and ring finger (CHFR) methylation.

Results: Data on 198 patients is available. Median age 62 years (38-80); males: 83.8%; smokers: 77.8%; PS 0-1: 95.3%; adenocarcinoma, 48.9% / squamous, 32.8%; stage IIIB: 16.7%, IV: 83.3%. Median cycles: 4 (1-12). Hematological toxicities (%p): neutropenia grade 3-4, 17.2%; thrombocytopenia grade 3-4, 1%; anemia grade 3, 2%. Febrile neutropenia appeared in 14 cycles / 10 patients (1.8%/5,1%). Non-hematological toxicities (%p): pulmonary grade 3-4, 5.5%; nausea/vomiting grade 3-4, 8.1%; asthenia grade 3, 13.2%; pain grade 3, 6.6%; infection grade 3, 4.1%; neurotoxicity grade 3, 0.5%. Efficacy in evaluable population: CR, 2.3%; PR, 30.8%; ORR, 33.1% (95% CI, 26.1% to 40.2%); SD, 39.7%. Median follow up of 6.7 months, median survival for the whole population was 9 months (m), progression free survival 5.07 m, event free survival 4.8 m, 1-year survival 39.9%.

Conclusions: This trial confirms that CDDP/VRB is effective as first-line therapy, presenting a favourable toxicity profile in patients with advanced NSCLC. A complete genomic analysis is ongoing.