14:00 - 15:00 h.	Almuerzo
15:00 - 16:30 h. Sala C	**Mesa - Debate:** **Tratamiento del mesotelioma pleural**

Moderadores: Dr. Juan José Mafé Madueño; Dr. José M. Galbis Caravajal

Ponentes	15:00 h.	**Cirugía del mesotelioma** Dr. Laureano Molins López-Rodó
	15:15 h.	**Tratamientos combinados** Dra. Regina Gironés Sarrió
	15:30 h.	**CONFERENCIA MAGISTRAL:** **La experiencia del Instituto Nacional del Tumori en mesotelioma peritoneal** Dr. Marcelo Deraco Instituto Nacional del Tumori. Milán. Italia.
	16:00 h.	Debate

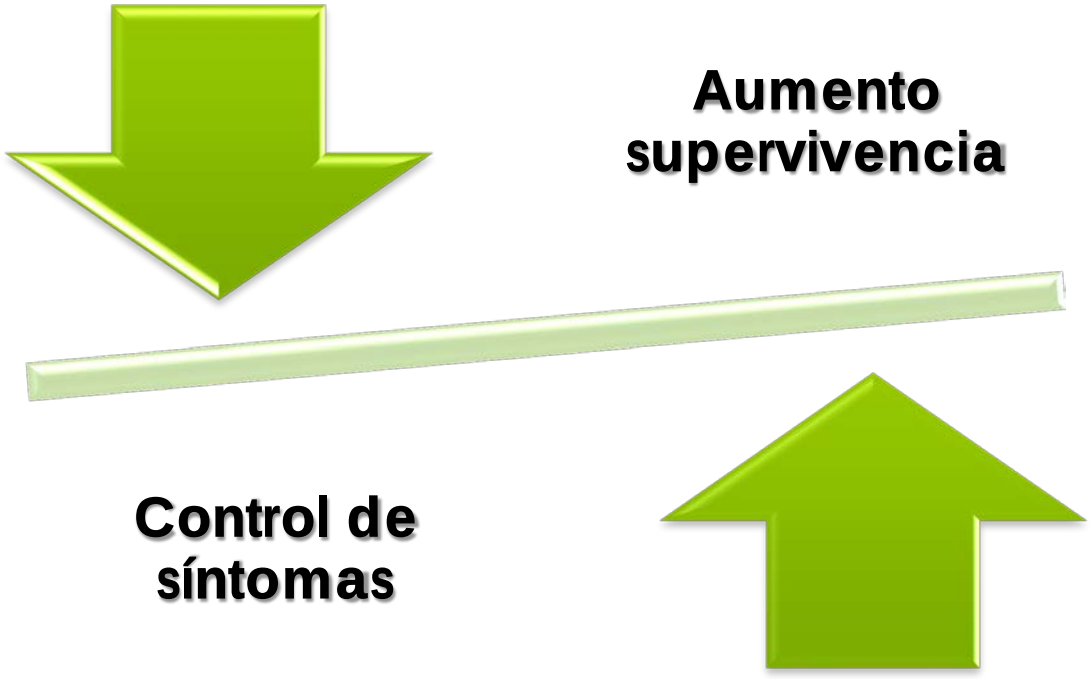
Jornada de Cirugía Torácica

patrocina: Johnson&Johnson Medical

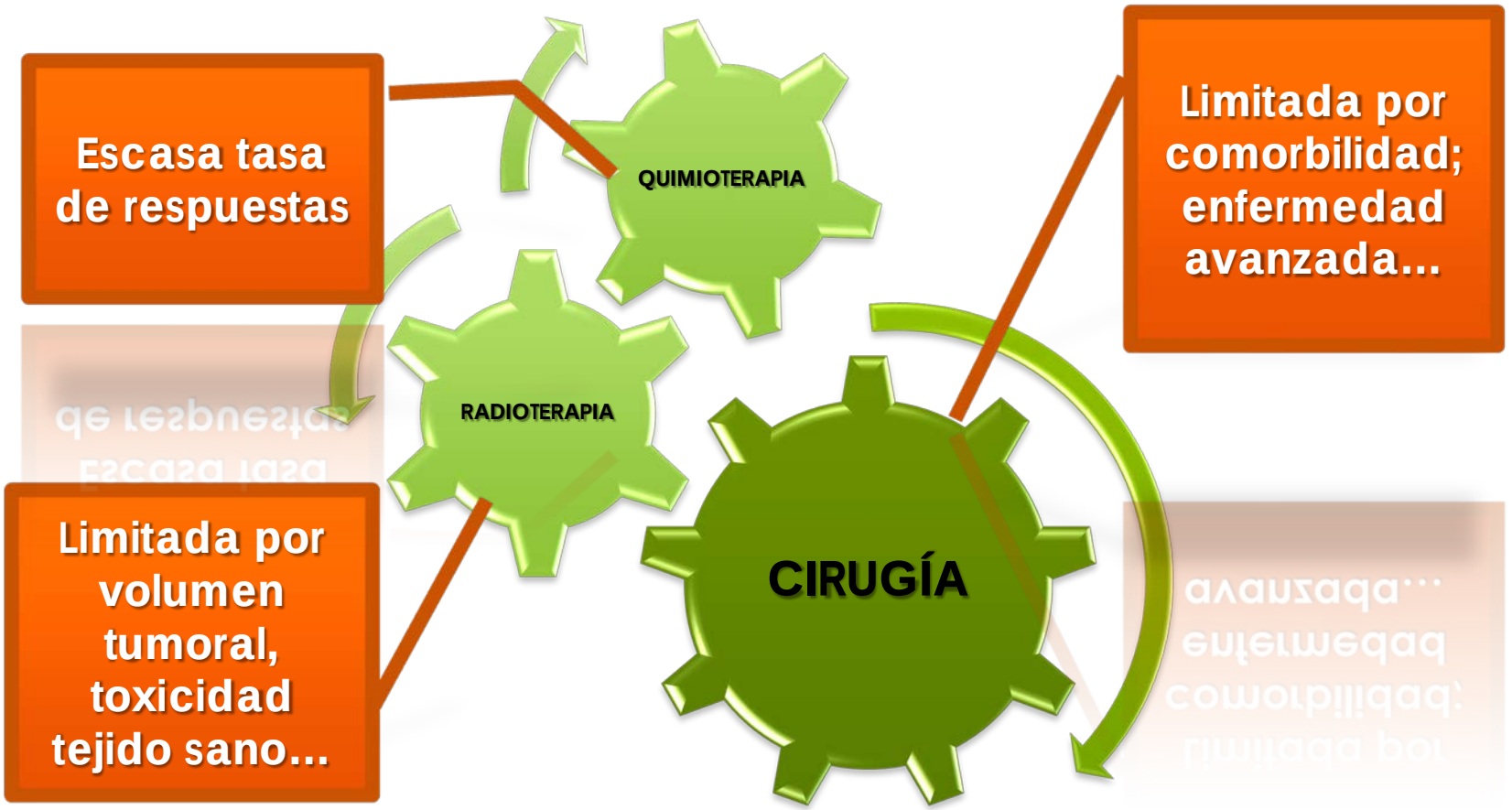
¿Dónde estamos?

- 80% mesoteliomas son pleurales
- Asbesto
- Incremento incidencia
- Nihilismo: escasa respuesta
- Mediana de supervivencia:
  - 10-17 meses des de la aparición de los síntomas
  - 13 meses des del diagnóstico

Objetivo del tratamiento

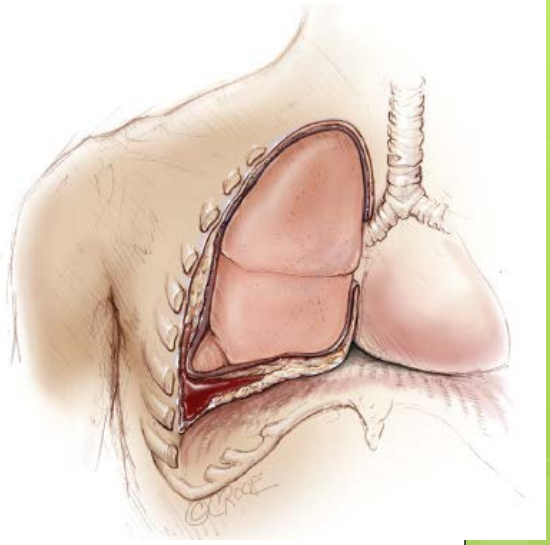


Opciones terapéuticas



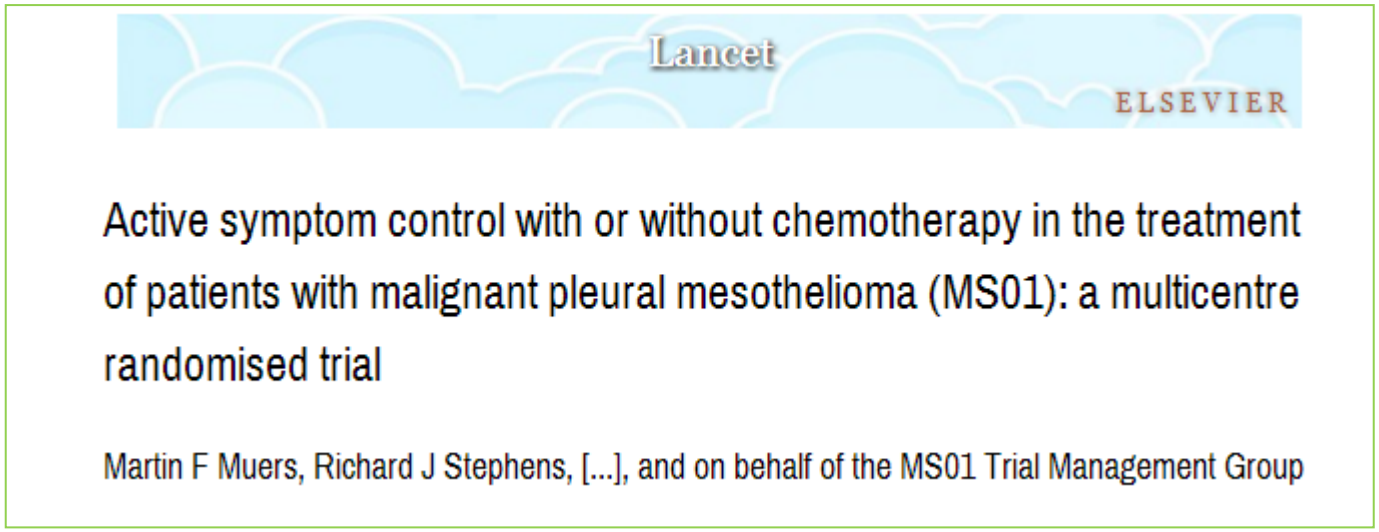
Las modalidades únicas: cirugía, quimioterapia, radioterapia, no han conseguido demostrar impactos en la supervivencia: MANEJO MULTIDISCIPLINAR

Avances



- Estadificación más adecuada
- Selección pacientes
- Mejoras en las técnicas quirúrgicas
- Nuevas técnicas de radioterapia (IMRT)
- Tratamientos antifolatos
  (pemetrexed, raltitrexed)
- Estudio molecular/nuevas dianas

Avances en quimioterapia



- Antifolatos:
  - Pemetrexed
  - Raltitrexed

Pemetrexed disodium

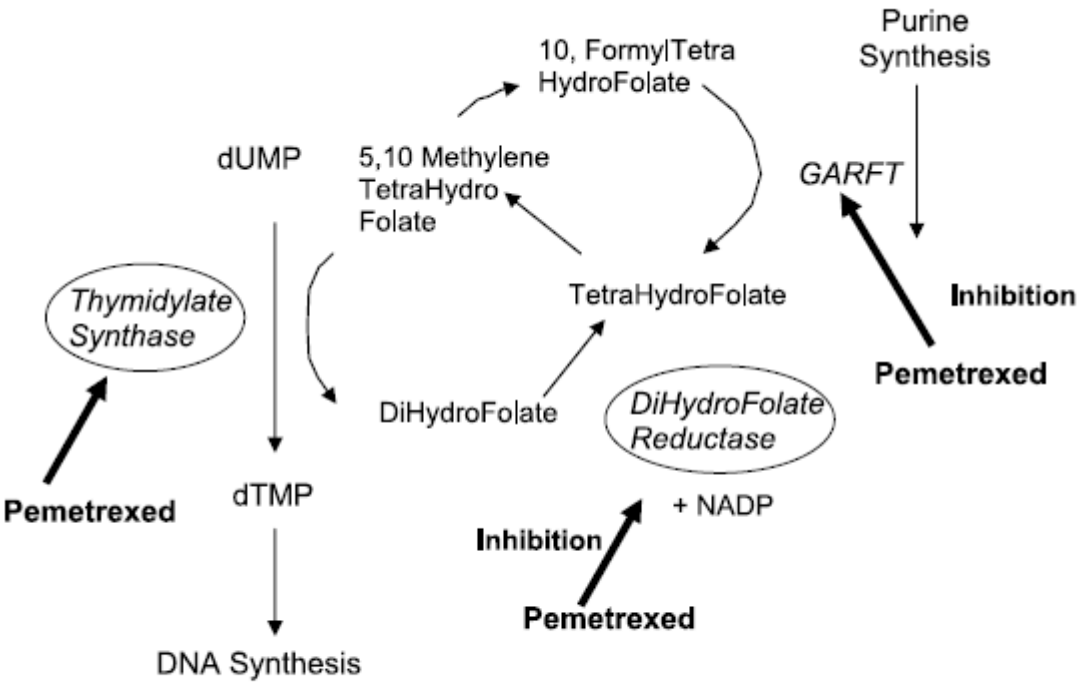
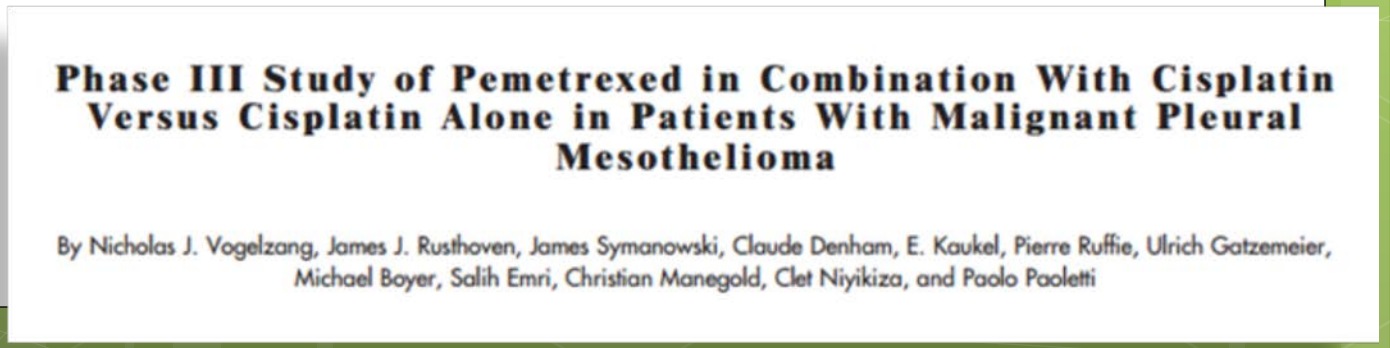


Fig. 1 Inhibition of multiple folate-requiring enzymes by pemetrexed and its polyglutamated metabolites.

Estudio fase III

- Pacientes con diagnóstico de mesotelioma pleural maligno, no candidatos a cirugía y con enfermedad medible
- Criterios para estadificación del International Mesothelioma Interest Group (IMIG)
- Excluyen pacientes irradiados o con quimioterapia previa (salvo si ésta ha sido utilizada para pleurodesis)



Phase III Study of Pemetrexed in Combination With Cisplatin Versus Cisplatin Alone in Patients With Malignant Pleural Mesothelioma

By Nicholas J. Vogelzang, James J. Rusthoven, James Symanowski, Claude Denham, E. Kaukel, Pierre Ruffie, Ulrich Gatzemeier, Michael Boyer, Salih Emri, Christian Manegold, Clet Niyikiza, and Paolo Paoletti

Table 1 Summary of patient characteristics

Patient characteristics	Randomized and treated patients		Fully supplemented patients	
	Pemetrexed + cisplatin (n = 226)	Cisplatin (n = 222)	Pemetrexed + cisplatin (n = 168)	Cisplatin (n = 163)
Age (y)				
Median (range)	61 (29-85)	60 (19-84)	60 (29-85)	60 (19-82)
Gender (%)				
Male	184 (81.4)	181 (81.5)	136 (81.0)	134 (82.2)
Female	42 (18.6)	41 (18.5)	32 (19.0)	29 (17.8)
Origin (%)				
Caucasian	204 (90.3)	206 (92.8)	150 (89.3)	153 (93.9)
Hispanic	11 (4.9)	12 (5.4)	10 (6.0)	7 (4.3)
Asian	10 (4.4)	4 (1.9)	7 (4.2)	3 (1.8)
African descent	1 (0.4)	0	1 (0.6)	0
Stage at entry (%)				
I	16 (7.1)	14 (6.3)	15 (8.9)	12 (7.4)
II	35 (15.6)	33 (15.0)	27 (16.2)	27 (16.8)
III	73 (32.4)	68 (30.6)	51 (30.5)	49 (30.4)
IV	101 (44.9)	105 (47.2)	74 (44.3)	73 (45.3)
Unspecified	1 (0.4)	2 (0.9)	1 (0.6)	2 (1.2)
Diagnosis/histology* (%)				
Epithelial	154 (68.1)	152 (68.5)	117 (69.6)	113 (69.3)
Mixed	37 (16.4)	36 (16.2)	25 (14.9)	25 (15.3)
Sarcomatoid	18 (8.0)	25 (11.3)	14 (8.3)	17 (10.4)
Other	17 (7.5)	9 (4.1)	12 (7.1)	8 (4.9)
Baseline Karnofsky Performance Scale (%)				
70-80	109 (48.2)	97 (43.7)	83 (49.4)	69 (42.3)
90-100	117 (51.8)	125 (56.3)	85 (50.6)	94 (57.7)

*Only 67% of the patients had the histologic diagnosis of malignant mesothelioma confirmed by independent review. After independent review epithelial, mixed, and sarcomatoid were the only subtypes; there were no "other."

Beneficio en supervivencia

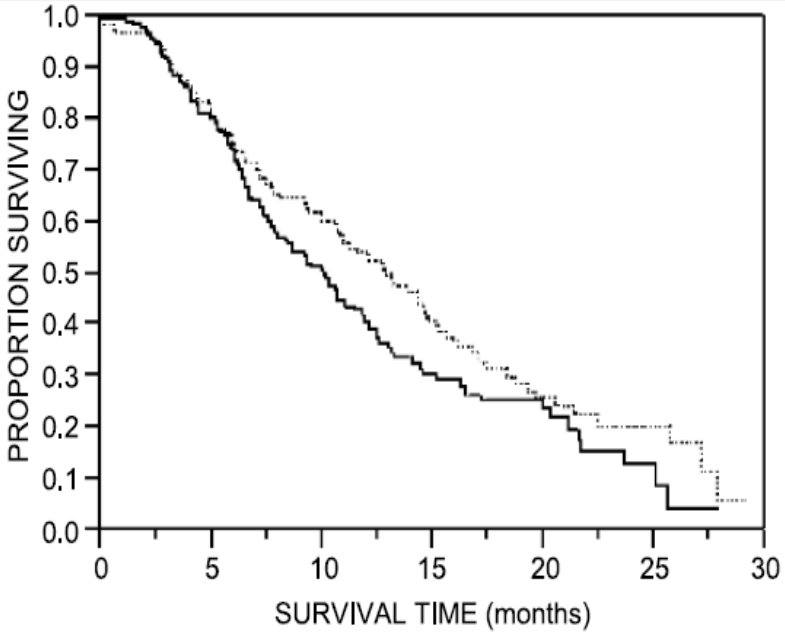


Fig. 6 Kaplan-Meier survival times for all patients with confirmed mesothelioma diagnosis (n = 303).

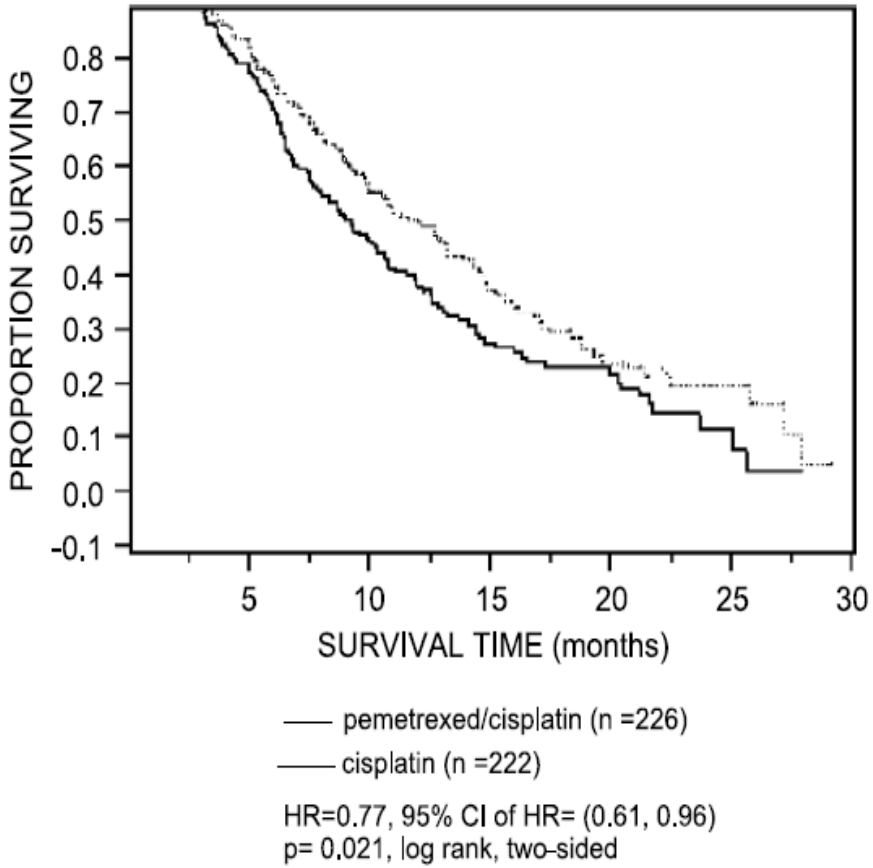


Fig. 4 Kaplan-Meier estimates of survival time for all randomized and treated patients (n = 448).

toxicidad

Table 4 Adverse events in fully supplemented patients receiving pemetrexed and cisplatin

	All reported adverse events regardless of causality					
	Pemetrexed + cisplatin (*n* 168)			Cisplatin (*n* 163)		
	All grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
Laboratory						
Hematologic						
Neutropenia	58.3	19.0	5.4	16.0	2.5	0.6
Leukopenia	55.4	13.7	1.8	19.6	0.6	0
Anemia	32.7	5.4	0.6	14.1	0	0
Thrombocytopenia	26.8	4.2	1.2	9.8	0	0
Renal						
Creatinine	15.5	0.6	0	12.3	1.2	0
Renal failure	2.4	0	0.6	1.2	0	0
Hepatic						
Aspartate aminotransferase (SGOT)	8.3	0	0	8.6	0.6	0
Clinical						
Constitutional symptoms						
Fatigue	80.4	16.7	0	73.6	12.3	0.6
Fever	17.3	0	0	8.6	0	0
Other constitutional symptoms	10.7	1.8	0.6	8.0	0.6	0.6
Cardiovascular general						
Other cardiovascular general	11.3	0	1.2	11.0	1.8	0
Thrombosis/embolism	7.1	4.2	1.8	3.7	2.5	1.2
Gastrointestinal						
Nausea	83.9	11.3	0.6	78.5	5.5	0
Vomiting	57.7	10.1	0.6	51.5	3.7	0.6
Constipation	44.0	2.4	0.6	39.3	0.6	0
Anorexia	34.5	2.4	0	25.2	0.6	0
Stomatitis/pharyngitis	28.0	1.8	1.2	8.6	0	0
Diarrhea without colostomy	26.2	3.6	0	16.0	0.6	0
Other gastrointestinal	19.0	1.2	0.6	16.0	0.6	0
Dehydration	7.1	3.0	1.2	1.2	1.2	0
Dysphagia/esophagitis/odynophagia	6.0	1.2	0	5.5	0	0
Pulmonary						
Dyspnea	65.5	9.5	0.6	62.0	4.9	1.8
Other pulmonary	20.2	2.4	0	19.0	1.2	0.6
Pain						
Chest pain	39.9	7.7	0.6	30.1	4.9	1.2
Tumor pain	18.5	3.6	0.6	14.7	3.7	0.6
Neurology						
Neuropathy/sensory	17.3	0	0	14.7	0.6	0
Mood alteration/depression	13.7	1.2	0	9.2	0.6	0
Infection/febrile neutropenia						
Infection without neutropenia	11.3	1.2	1.2	4.3	0	0
Infection with grade 3 or 4 neutropenia	6.0	0.6	0	4.3	0	0
Infection/febrile neutropenia other	3.0	1.2	0	1.8	0	0
Febrile neutropenia	0.6	0.6	0	0.6	0	0
Immune						
Allergic reaction/hypersensitivity	2.4	0	0	0.6	0	0
Dermatology/skin						
Rash/desquamation	22.0	0.6	0	9.2	0	0

Raltitrexed

VOLUME 23 · NUMBER 28 · OCTOBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY

Randomized Phase III Study of Cisplatin With or Without Raltitrexed in Patients With Malignant Pleural Mesothelioma: An Intergroup Study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada

Jan P. van Meerbeeck, Rabab Gaafar, Christian Manegold, Rob J. Van Klaveren, Eric A. Van Marck, Mark Vincent, Catherine Legrand, Andrew Bottomley, Channa Debruyne, and Giuseppe Giaccone

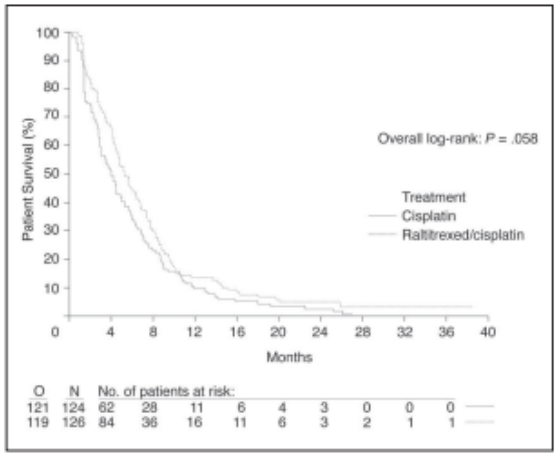


Fig 4. Kaplan-Meier estimates of progression-free survival time for all patients according to treatment arm.

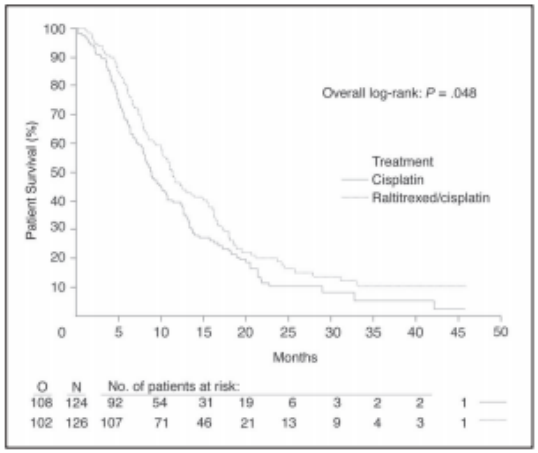


Fig 3. Kaplan-Meier estimates of overall survival time for all patients according to treatment arm.

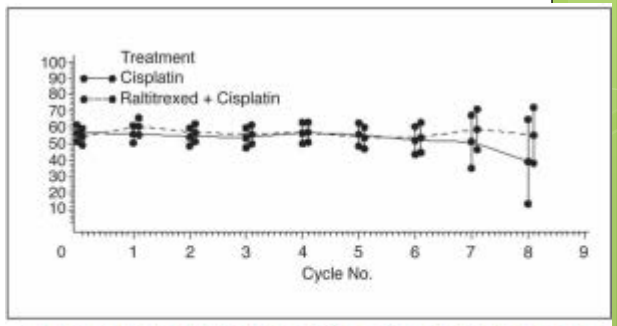


Fig 2. Means and standard deviations of global health-related quality of life per treatment arm over time on treatment. No time trend or treatment over time interaction was detected.

Table 2. Randomized trials with cisplatin and antifolates in MPM

Study	Regimen	*n*	RR (%)	mTTP (months)	mSv (months)	1-Yr Sv (%)
Vogelzang et al. [11]	Cisplatin + pemetrexed	226	41.3	5.7	12.1	50.3
	Cisplatin	222	16.7	3.9	9.3	38.0
			$p < .0001$	$p = .001$	$p = .02$	$p = .012$
van Meerbeeck et al. [12]	Cisplatin + raltitrexed	126	23.6	5.3	11.4	46.2
	Cisplatin	124	13.6	4.0	8.8	39.6
			$p = .056$	$p = .058$	$p = .0483$	$p = .0483$

Abbreviations: MPM, malignant pleural mesothelioma; mTTP, median time to progression; mSv, median survival; RR, response rate; Sv, survival rate.

- Combinacion carboplatino pemetrexed es mejor tolerado y podría ser una opción para pacientes con comorbilidad. Datos de un uso expandido con 1704 pacientes

Table 3. Studies of second-line chemotherapy in MPM

Study	Regimen	*n*	RR (%)	mTTP (months)	mSv (months)
Pemetrexed-naïve patients					
Giaccone et al. [53]	ZD0437 (platinum analogue)	47	12[a]	2.5	6.7
Porta et al. [54]	Raltitrexed + oxaliplatin	14	0	1.9	3.2
Sorensen et al. [55]	Pemetrexed with or without carboplatin	39	23	4.9	6.5
Jassem et al. [56][b]	Pemetrexed	123	19.2	3.8	8.6
Pemetrexed-pretreated patients					
Zucali et al. [58]	Gemcitabine + vinorelbine	28	7.4	2.8	NR
Serke et al. [59]	Oxaliplatin with or without gemcitabine	18	22[a]	NR	NR

[a]Responses reported as "minor responses."
[b]Randomized trial of pemetrexed versus best supportive care (data reported for the pemetrexed arm only).
Abbreviations: MPM, malignant pleural mesothelioma; mSv, median survival; mTTP, median time to progression; NR, not reported; RR, response rate.

- Pemetrexed: retratamiento
- Vinorelbina
- Gemcitabina

Estadios operables: ¿podemos aplicar estos avances en estadios iniciales?: TMT

Systematic Review

Systematic review of trimodality therapy for patients with malignant pleural mesothelioma

Christopher Cao[1,2,3], David Tian[1], Con Manganas[2], Phoebe Matthews[1], Tristan D. Yan[1,3,4]

[1]The Systematic Review Unit, Collaborative Research (CORE) Group, Sydney, Australia; [2]Department of Cardiothoracic Surgery, St George Hospital, Sydney, Australia; [3]The Baird Institute for Applied Heart and Lung Surgical Research, Sydney, Australia; [4]Department of Cardiothoracic Surgery, Royal Prince Alfred Hospital, Sydney, Australia

TMT

Systematic Review

Systematic review of trimodality therapy for patients with malignant pleural mesothelioma

Christopher Cao[1,2,3], David Tian[1], Con Manganas[2], Phoebe Matthews[1], Tristan D. Yan[1,3,4]

- 16 estudios:

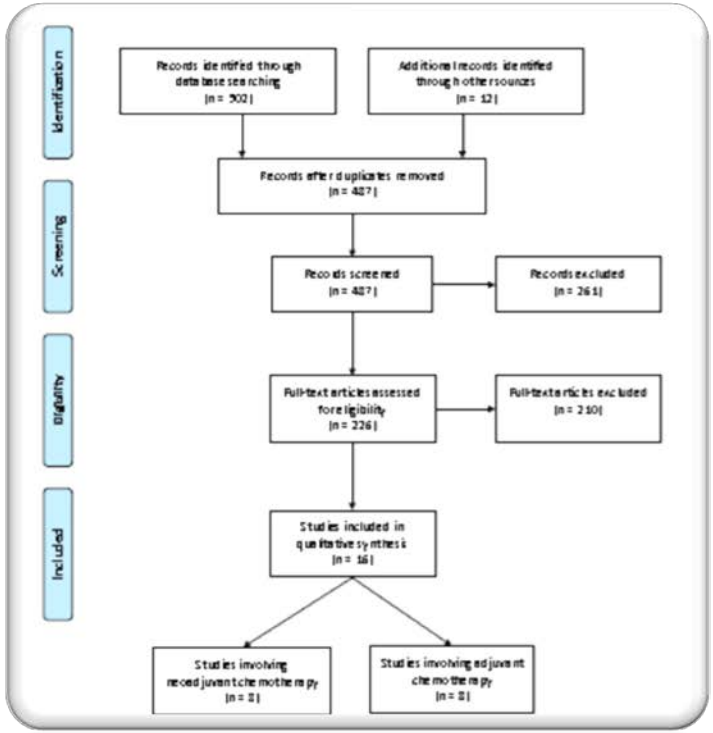
1 aletorizado, 5 series prospectivas

- Quimioterapia adyuvante o neoadyuvante, EPP, Radioterapia
- Mediana de supervivencia:

  12.8-46.9* meses
- SLE 10-16.3 meses
- Mortalidad perioperatoria:

  0-12.5%
- Morbilidad perioperatoria:

  50-82.6%



SG 16.8-25.5 m

SG 19-24 m

Adyuvancia

- Estudios retrospectivos
- Esquemas no estandarizados de tratamiento

Neoadyuvancia

Ventajas

- Posibilidad de completar tratamiento (57-71%)
- Test sensibilidad (TR: 48%)
- Mejorar resecabilidad

Inconvenientes:

- Riesgo progresión
- Dificultad evaluación respuesta
- Riesgo quirúrgico

Adyuvancia: Brigham and Women's Hospital

Table 4. Trimodality therapy in MPM: Brigham's study [ref 88]

Prognostic variable	*n*	mSv (months)	2-Yr Sv (%)	5-Yr Sv (%)	Odds ratio (CI)
Histology					
Epithelial	103	NR	52	21	
Mixed/sarcomatous	73		16	0	3.0 (2.0–4.5)
Resection margins					
Negative	66	NR	44	25	
Positive	110		33	9	1.7 (1.2–2.6)
Extrapleural nodes					
Negative	136	NR	42	17	
Positive	40		23	0	2.0 (1.3–3.2)
Three positive prognostic factors	31	51	68	46	-
All patients	176	19	38	15	-

Abbreviations: CI, 95% confidence interval; MPM, malignant pleural mesothelioma; mSv, median survival; NR, not reported; Sv, survival rate.

Table 5. Studies of neoadjuvant chemotherapy in MPM

Study	*n*	Stage	Chemotherapy regimen	Postoperative RT	mSv (months)	Perioperative morbidity
Weder et al. [125][a]	19	T1–3 N0–2	Cisplatin + gemcitabine	High-risk areas (45–60 Gy)	23 months	37.5%
Weder et al. [126][b]	61	T1–3 N0–2	Cisplatin + gemcitabine	High-risk areas (45–60 Gy)	23 m	NR
Opitz et al. [132][c]	72	T1–3 N0–2	Cisplatin + gemcitabine or cisplatin + pemetrexed	Optional (75% treated)	23	62% (mortality 3.2%)[d]
Flores et al. [128]	21	T3–4 N0–2	Cisplatin + gemcitabine	Hemithoracic (54 Gy)	33.5 m	No grade 4 toxicity
Rea et al. [129]	21	I-III	Carboplatin + gemcitabine	Hemithoracic (45 Gy)	24% 5 años	

[a]Single-center pilot trial.
[b]Multicenter trial (SAKK 17/00).
[c]Single-center retrospective analysis including patients from previous studies.
[d]Data reported in an analysis on 63 patients published separately [127].
Abbreviations: MPM, malignant pleural mesothelioma; mSv, median survival; NR, not reported; RT, radiotherapy.

VOLUME 27 · NUMBER 18 · JUNE 20 2009

JOURNAL OF CLINICAL ONCOLOGY

Multicenter Phase II Trial of Neoadjuvant Pemetrexed Plus Cisplatin Followed by Extrapleural Pneumonectomy and Radiation for Malignant Pleural Mesothelioma

Lee M. Krug, Harvey I. Pass, Valerie W. Rusch, Hedy L. Kindler, David J. Sugarbaker, Kenneth E. Rosenzweig, Raja Flores, Joseph S. Friedberg, Katherine Pisters, Matthew Monberg, Coleman K. Obasaju, and Nicholas J. Vogelzang

Table 1. Baseline Demographics and Clinical Characteristics of Intent-to-Treat Population

Characteristic	No. of Patients (N = 77)	%
Age, years		
Median	63.0	
Range	34-78	
Sex		
Male	56	72.7
Female	21	27.3
Race		
White	71	92.2
Other	6	7.8
ECOG PS		
0	28	36.4
1	47	61.0
2	2	2.6
Histology		
Epithelial	62	80.5
Mixed	2	2.6
Sarcomatoid	1	1.3
Indeterminate	12	15.6
Clinical stage		
IA	3	3.9
IB	3	3.9
II	33	42.9
III	35	45.5
IV	1	1.3
Unavailable	2	2.6

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

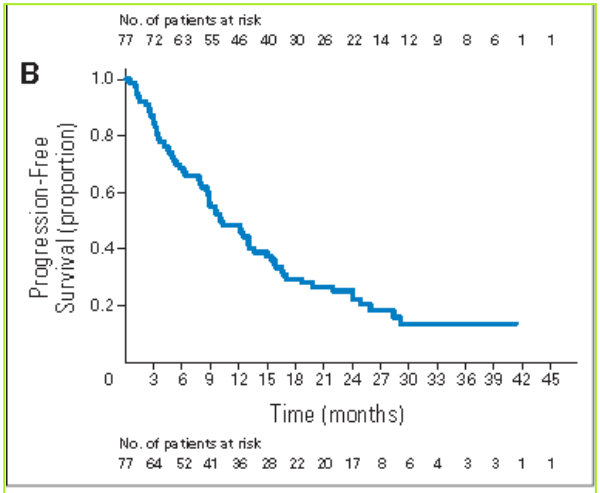
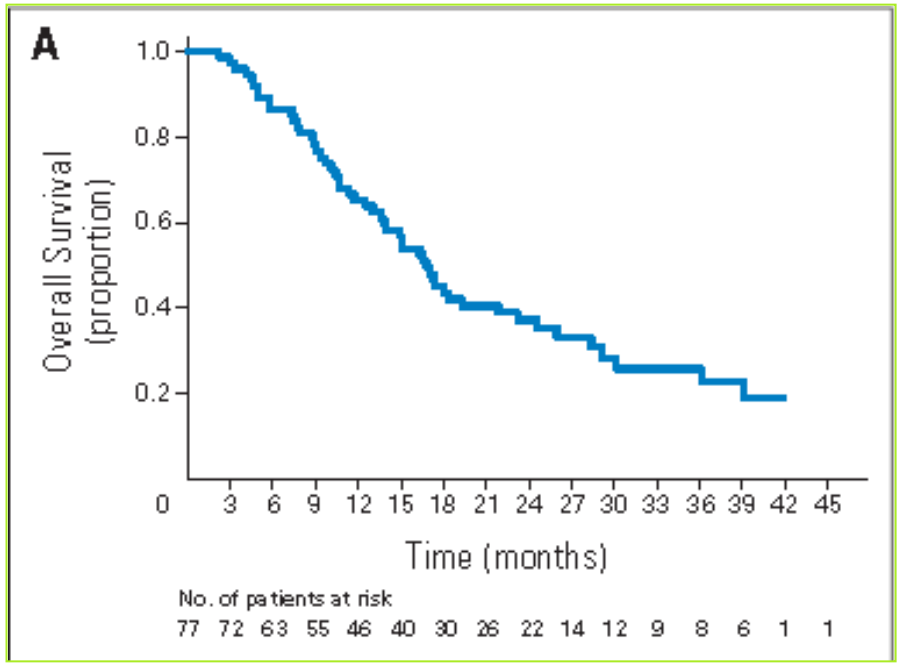


Fig 2. (A) Kaplan-Meier overall survival, intent-to-treat (ITT) population (median, 16.8 months; 95% CI, 3.6 to 23.2 months). (B) Kaplan-Meier progression-free survival, ITT population (median, 10.1 months; 95% CI, 8.6 to 15.0 months).



Papel de la cirugía: MARS trial

THE LANCET Oncology

Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study

Prof Tom Treasure MD [a], Loic Lang-Lazdunski MD [b], David Waller FRCS [CTh] [d], Prof Judith M Bliss MSc [f], Carol Tan FRCS [CTh] [g], James Entwisle FRCR [h], Michael Snee DM [i], Mary O'Brien MD [i], Gill Thomas FRCR [k], Prof Suresh Senan FRCR [l], Prof Ken O'Byrne MD [m], Lucy S Kilburn MSc [f], James Spicer MRCP [c], David Landau FRCR [c], John Edwards FRCS [CTh] [n], Gill Coombes RGN [f], Liz Darlison RGN [e], Prof Julian Peto DSc [o], for the MARS trialists‡

TMT

- Tras la revisión, se concluye que EPP puede realizarse sin elevada mortalidad en centros experimentados
- Las tasas de supervivencia son inconsistentes entre los estudios
- Se necesita más evidencia para realizar conclusiones definitivas respecto al papel de la cirugía. El estudio MARS supone un gran esfuerzo a pesar de sus resultados

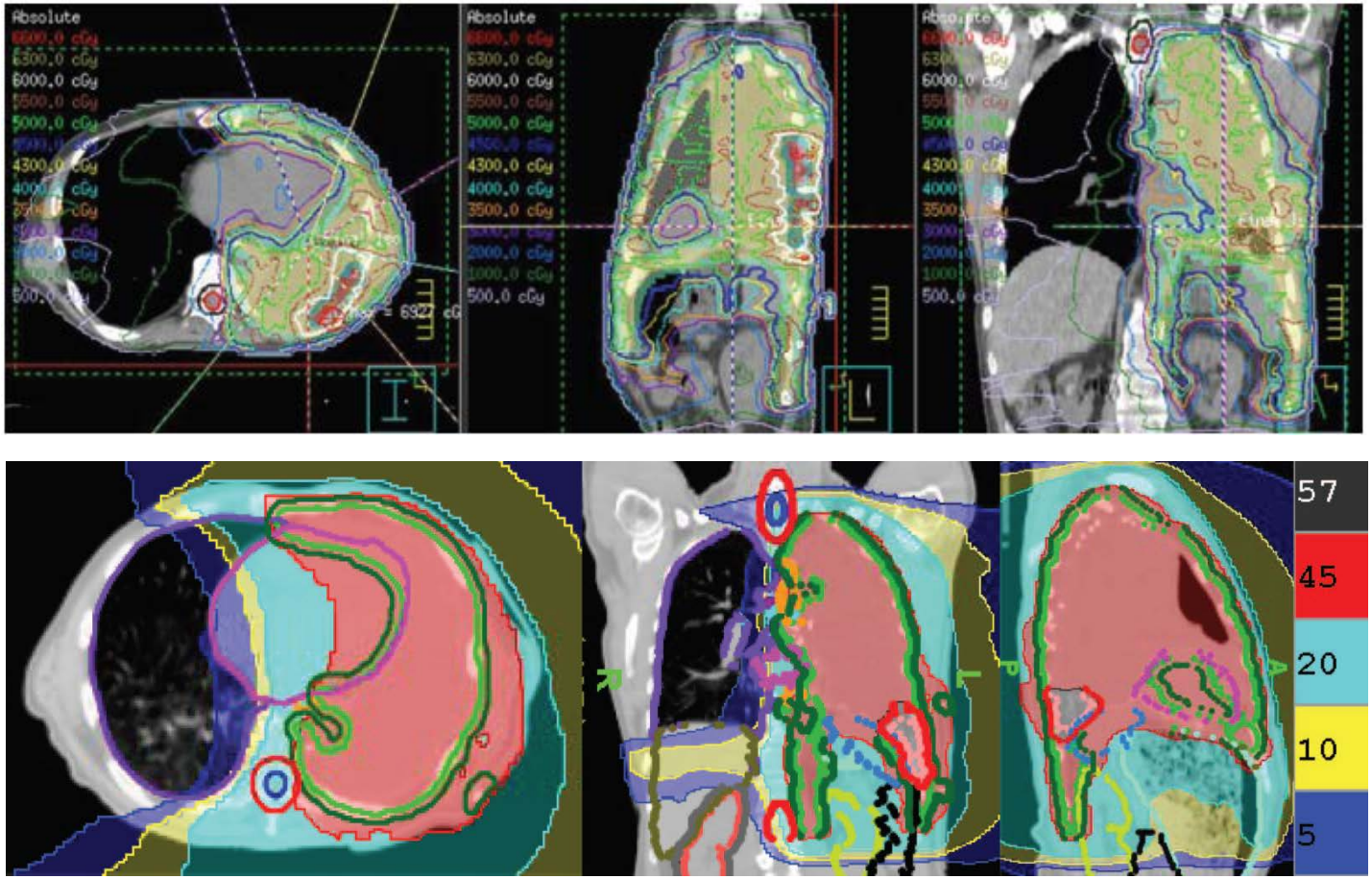
¿Qué pacientes se beneficiarían de esta modalidad?

- Análisis retrospectivo de 560 pacientes: factores asociados con la supervivencia: EPP, experiencia del cirujano, pemetrexed
- Recomendación EPP: pacientes que requieren resección completa: buen PS, sin comorbilidad, estadio II-III, histología favorable (epiteloide, no N2)
- No se recomendaría EPP para pacientes de alto riesgo: histología desfavorable: sarcomatoide, tumores mixtos, persistencia N2, estadio IV

RT

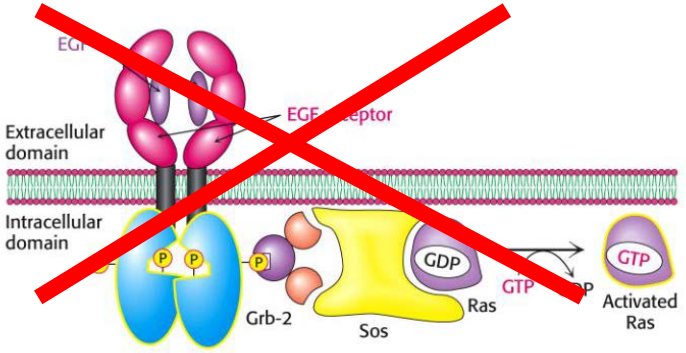
- Tampoco está bien definido el papel de la RT en MPM
- Tres estudios aleatorizados analizan el papel de la Radioterapia externa para prevenir implantes, con resultados contradictorios

IMRT

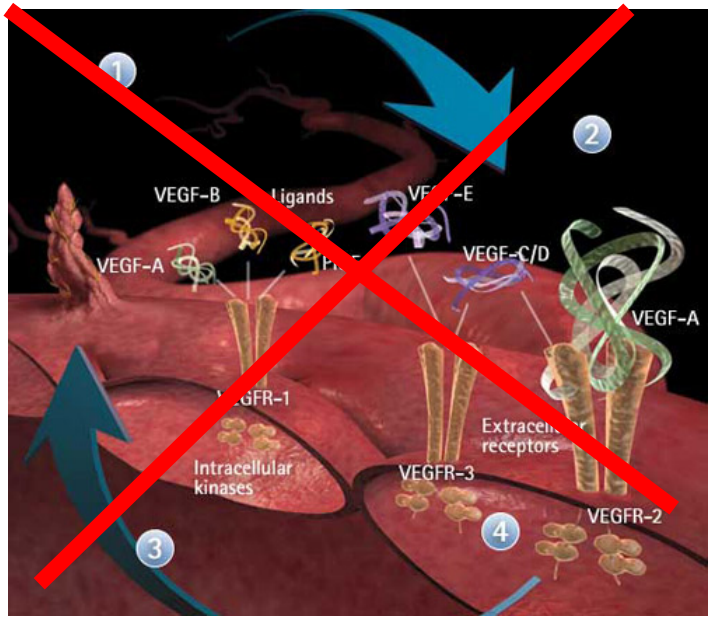

Absolute
6300.0 cGy
6000.0 cGy
5500.0 cGy
5000.0 cGy
4300.0 cGy
4000.0 cGy
3500.0 cGy
2000.0 cGy
1000.0 cGy
500.0 cGy
57
45
20
10
5

Tratamientos diana

- EGFR está sobre-expresado en el mesotelioma



- VEGF y PDGF son factores de crecimiento autocrinos importantes en esta neoplasia



antiangiogénicos

- PTK787, talidomida: sin actividad
- SU5416: inhibidor del receptor VEGF Flk-1, tiene algo de actividad con excesivo riesgo de trombosis
- Bevacizumab: en evaluación en un estudio fase II con cisplatino-gemcitabina. Cierre del reclutamiento, pendiente de resultados definitivos. Datos: SLP de 6.4 meses, mediana de SG de 15.7 meses y tasa de SG a 1 año del 60.1%. Los niveles basales de VEGF predicen SLP y SG pero no la respuesta

Br J Cancer. 2013 Aug 6;109(3):552-8. doi: 10.1038/bjc.2013.368. Epub 2013 Jul 16.

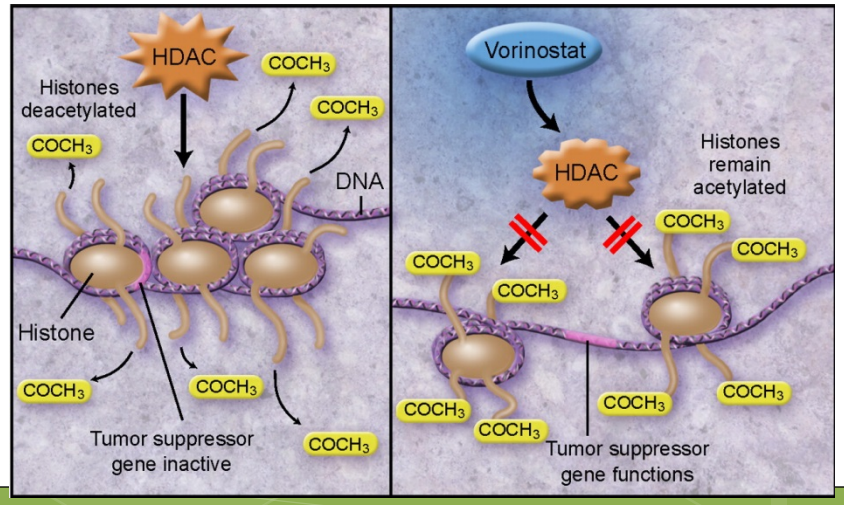
Phase II study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma.

Ceresoli GL, Zucali PA, Mencoboni M, Botta M, Grossi F, Cortinovis D, Zilembo N, Ripa C, Tiseo M, Favaretto AG, Soto-Parra H, De Vincenzo F, Bruzzone A, Lorenzi E, Gianoncelli L, Ercoli B, Giordano L, Santoro A.

Department of Medical Oncology, Cliniche Humanitas Gavazzeni, Bergamo, Italy. giovanni_luca.ceresoli@gavazzeni.it

- Sorafenib: inhibidor tirosin kinasa de VEGFR-2, PDGFR-b y B-Raf. Fase II con 51 pacientes en 1ª línea o tras pemetrexed, RP en 4.7%, mediana de tiempo hasta fallo de tratamiento de 4.1 meses y SG de 6.3 meses

- Vorinostat: fase I: inhibidor de histonas-deacetilasa. TR: 20%. Pediente de un fase III aleatorizado doble ciego con placebo
- Fase II internacional en marcha con bortezomib



rope and in the U.S. [130, 131]. Very preliminary data suggest that this regimen may produce treatment outcomes that are superior to those seen with cisplatin plus gemcitabine [132].

Conclusions

MPM remains a difficult disease to treat. No standard therapy exists, and randomized studies are lacking [133]. However, in the last few years, much progress has been made in this field.

The combination of pemetrexed with a platinum derivative can now be considered as standard in unresectable disease. Schedules with carboplatin should be considered, particularly in elderly and unfit patients. Although there is no consensus about the optimal duration of first-line chemotherapy, no evidence of a benefit with prolonged administration exists, and the use of six courses seems a reasonable option. Pemetrexed or a pemetrexed-containing regimen should be administered as second-line therapy in patients who have not received it as first-line treatment. Pemetrexed-pretreated patients should be enrolled ideally in dedicated prospective trials.

Radical surgery (EPP) and multimodality treatments are increasingly used, but the role of this aggressive approach should be further confirmed. Induction chemotherapy followed by surgery and adjuvant RT is promising. Clear, reproducible, and safe RT protocols are needed. Outside of clinical trials, multimodality treatments should be limited to patients with early (T1–T2) disease with no evidence of nodal involvement at the preoperative assessment. Careful patient staging and stratification based on the use of validated prognostic indexes [2, 3], and of new prognosticators such as FDG-PET [134], are essential to refer patients to the proper treatment and to avoid unnecessary and distressing treatments when they are not indicated.

Functional imaging, mainly with FDG-PET, is providing new insights into staging and response evaluation to chemotherapy and targeted agents in MPM.

Finally, advances in the knowledge of MPM molecular mechanisms hopefully will lead to the development of novel targeted agents for the treatment of advanced and early-stage disease.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

Conclusiones

- Manejo MPM controvertido
- Avances en enfermedad avanzada con nuevas opciones de quimioterapia
- Aplicación en estadios iniciales precisa de abordaje multidisciplinar, elección tratamiento trimodal en centros experimentados y pacientes seleccionados

MUCHAS GRACIAS