NUEVOS MEDICAMENTOS PARA EL TRATAMIENTO DEL CANCER
QUIMIOTERAPIA

Actualizacion Dic 2002
Nueva actualizacion Dic 2009

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1.- Agentes interactivos con DNAs

DNA repair of bifunctional adducts cause double strand breaks or single strand gaps leading to apoptosis or cell death. It is by itself a therepeutic field. Repair of genotoxic lesions includes: 1. Direct repair, in case of nitrosoureas, based in O6 methylguanine methyltransferase (MGMT), use a mechanism that can be enhanced by O6 benzylguanine or O6 methylguanine exposure prior to nitrosourea treatment, causing a blockade of MGMT and the inhibiting repair od DNA damage. 2. Base excission repair based in methylpurine DNA glusosylase (MPG) first and then in endonucleases. 3. Nucleotide excission repair, usually in CDDP damage, is based in ATP dependent 27 or 28 oligo removal. 4. Mismatch repair, in nitrogen mustard. 5. Postreplication repair mechanisms. Resistance is frequently multifactorial with decreased drug accumulation , increase in glutathione, increased efflux, increased activity of glutathione s-tranferase and metallothionan, altered metabolism & also increased tolerance to unrepaired damage, all of them contributing to drug resistance.

ALKYLATING AGENTS:

RB Jones (Cin Ca Res 2004;10:413-4). CPA metabolism in the liver correlates with its activity. Ring oxydation increaases phosphoramide mustard (active compound) while side chain oxydation decreses it and enhance dechloroethyl CPA (inactive). Also aldehyde dehydrogenase increases aldophosphamide/carboxyphosphamide both inactive. High dose CPA should be pharmacologically correlated.

DH Salinger et al (ClinCa Res 2006;12:4888-98). Bayesian real time dose adjustement of CPA in HD Chx-BMT, measuring AUC of metabolites (hydroxycyclophosphamide and carboxyethylphosphoramide).

S Ammons et al (Neoplasia 2007;9:625-33). Gluofsfamide (iphosphoramide mustard similar to iphosphamide), combined with Gemcitabine quite active in pancreatic cancer model. Hypothesis is that Gemcitabine inhibits double strand DNA repair. Can it be traslated to RT toxicity?).

O6 Benzylguanidine. Inhibe O6 alkylguanine alkyltransferase y aumenta la toxicidad de las nitrosoureas. Produce deplecion enzimatica a dosis 10-120 mg/m2, que dura hasta una semana. Combinado a BCNU la dosis de esta debe reducirse a 30 mg/m2 (no respuesta en gliomas, tal vez porque no consigue concentraciones adecuadas en el SNC a esta dosis).

L Liu and SL Gerson (Clin Ca Res 2006;12:328-31). Target modulation of MGMT: 1. Silencing due to CpG hypermethylation in promoter region, oberved in gliomas, pre-dictive of response. 2. Depletion of O6BG, enhancer of NU´s (BCNU 120 mg/m2 corre-late with 40 mg/m2). 3. Translation of MGMT into marrow cells. 3. Inactivation of MGMT & base excission repair (with Methoxyamine) have synergism together with BCNU.

Tallimustine (PNU 152241). DNA minor groove binder. No es un alquilante. En estudios de fase I la toxicidad es neutropenia y hepatica. MRD: 200 ug/m2/dx3 q 4 sem.

Rebeccamycin (NSC 655649). Inhibidor de Topo II. Tiene circulacion enterohepatica. Resultados impresionantes en Fase I en cancer del tracto biliar (1 RP+4 NC entre5 pacientes, con duracion media de 5-10 meses) Dosis recomendables: 188 mg/m2/d x 5; 500-572 mg/m2 q 3 sem. RO: colangio, vesicula biliar, ovario, sarcoma.

G Borthakur et al (Cancer 2008;113:360-6). XL119 (Rebeccamycin analog) Phase I: N=31 with MDS and AL). 140-260 mg/m2/d x 5 q 3 wk. MRD 200 mg/m2/d x 5 q 3 wk. Improvement in blast count in 5 patients.

Irofulven. Toxina derivada del hongo Omphalotus olearius. MRD 10,64 mg/m2 iv 5 min qdx5 q 4 sem. Toxicidad: trombopenia, neutropenia, renal. ! RP en cancer de pancreas resistente a 5 FU de duracion 7 meses.
Irofulven (Illudin) qd x 5. OR in pancreas, ovary, prostate, sarcoma, AML, thymoma (ASCO 2001)
Illudin, 24 mg/m2 5 min iv q 2 wks: OR renal, sarcoma, pancreas, prostate (ASCO 2001)
Illudin 21 mg/m2 5 min iv d 1& 8 q 3 wks: OR in sarcoma, ovary, prostate, melanoma (ASCO 2001)

J Alexandre et al (Clin Ca Res 2004;10:3377-85). Phase I Irofulven MRD 18 mg/m2 civi d 1 & 8 q 3 wk and 24 ng/m2 civi d 1 & 15 q 4 wk. Toxicity Thrombocytopenia, visual alterations (retinal toxicity). OR: 1CR ovary and 1 PR renal, 7 NC>4mo.

E Raymond et al (Clin Ca Res 2004;10:7566-74). Irofulven (6 hydroxymethyl-acylful-vene) derived from Illudins. N=277 in Phase I-II. 27% visual alterations (flashing lights 12%, blurred vision 9%, photosensitivity 4%). No grade III ocular toxicity at doses <0.5 mg/kg; at 0.5 mg/kg only 12% grade 2 toxicity . At <20 mg/m2 visual toxicity 8%. All visual toxicity is reversible, leading to abnormal visual field 58%. Recommend not to exceed 50 mg per dose in a 30 min iv infusion d 1 & 8 q 3 wk or d 1 & 15 q 4 wks.

MGI 114: Analogo de Illudin S, derivado del hongo Omphalotus illudens. Avtivo en tumores con alteraciones de helicase. Toxicidad nausea, vomito, mielodepresion y acidosis renal tubular reversible. Respuestas en Fase I: pancreas, ovario y prostata.

Anthracyclines:
PSC 833 + Liposomal Doxorubicin comparada a Doxo proporciona mejor tasa de respuestas en tumores resistentes a Doxo, sin modificar la

farmacocinética del fármaco. Muy prometedor (Krishna et al, Ca Res 1997;57:5246-53).

R Juliano (NEJM 2007;356:954-5). Tumors bugged with Chlostridium Novgi-NT secreting liposomase, can potentiate intratumoral degradation of liposome – doxorubicin. Hypoxia favors C. Novgi growth...

PK1 (conjugado de dox+copolimero). Actua por entrada intracelular por pinocitosis, el copolimero es cortado por lisozimas y doxo queda libre intracelularmente. MRD 280 mg/m2. No cardiotoxicidad hasta 1680 mgh/m2. Activo en Fase I (NSCLC, mama, colorectal)
DPPE+Doxorubicina. Antihistamínico H1, con estructura similar a Tamoxifeno, potencia la toxicidad de Doxo. En cancer de mama proporciona tasa de respuestas de 52% como agente unico (casi el doble que la doxo). Añade alguna toxicidad como vertigo e inestabilidad. Mejora a doxo!.
Desrazoxane, sistémico, en la extravasación de doxo, reduce la toxicidad local en 90% (en el raton) aunque se aplique 3 h mas tarde!.

Anthracenediones: Losoxanthrone: menos cardiotoxico que doxo, activo en ca de mama.
BBR 2778. Completado 3 Fase I. No cardiotoxico. MRD 240 mg/m2, q 3sem. Respuestas en pulmon, prostata, mama, linfoma, etc. Interesante.
MEN 10755

Ecteinascidin.
Mecanismo distinto de alquilantes, union a DNA-polimerasa (?). MRD 1500 mcg/m2 en infusión 214 h q 3 sem.. En infusión de 3 h, MRD 1200 mcg/m2. Respuestas en sarcoma, melanoma, colorectal, mama, gástrico, mesotelioma, ovario. Toxicidad: hepática, rabdomiolisis, hematologica (dexametasona mejora la toxicidad).

B Foronzesh et al (Clin Ca Res 2009;15:3591-9). Trabectedin wkly 0.61 mg/m2 1 h iv x 3 q 4 wks better than 0.58 mg/m2 in 3 h iv x 3 q 4 wk.

Aplidine 5 mg/m2 q 2 sem. Activo en neuroendocrino, medular de tiroides (ASCO 2002, 422)

Platin derivatives

BBR 3464 (platino trinuclear) activo en modelos resistentes a CDDP. MRD 1 mg/m2 q 3 sem. Toxicidad: fibrosis pulmonar, hematologica, diarrea. Respuestas en páncreas, colorectal. Acividad impresionante en xenografts de SCLC y ovario. Panel de 60 tumores de NCI Bethesda con espectro distinto de CDDP, interesante en tumores resistentes.

CDDP can go to fixed dose because the interpatient variability using body surface is so high (ASCO 2001, 266).

G. Kruh (Clin Ca Res 2003;9:5807-9). ATP7B, ATP7A & Ctr1 involved in Cooper transport metabolism are increased in tumor cell lines and relate to Pt resistance.

E. Reed (Clin Ca Res 2005;11:6100-2). Polynmorphism of ERCC1 codon 18 (J Vignier et al, Clin Ca Res 2005;11:6212-17) indicates pharmacological effect of Pt derivatives in DNA repair pathways.

*****LP Martin et al (Clin Ca Res 2008;14:1291-4). DNA repair: 1. Nucleotide excission repair (ERCC/XPF) mediate excission of DNA cisplatin adduct and then DNA polymerase repairs the defect. If ERCC is elevated less ORs to CDDP/CBDCA in NSCLC and ovarian cancer. 2. Mismatch repair pathway (MMR genes- mut protein complex) mediate excission of insertion/deletion loop or mismatch, & then DNA polymerase repairs defect. In case of MMR (MLH1) CDDP/CBDCA no response but LOHP still keeps effect because can not be repaired.**

******A Schmitt et al (Clin Ca Res 2009;15:3633-9). CBDCA Universal formula based in Cisplatin Clearance. CBDCA clearance (ml/min) = 117.8(Scr -umol/L-/75)e-0.450 .(cysC –mg/L-/1,00)e-0.385 . (Actual Body Weight/65)e+0.505 . (Age yo/56)e-0.366 . 0.847e sex –0 male and 1female- Useful for underweight and obese patients.**

SATRAPLATIN
H Choy et al (Clin Ca Res 2008;14:1633-8). Satraplatin is a po PT derivative when absorbed in the systemic circulation behaves as CDDP = cisammine dichloro (cyclohexylamine)Platinum II. Toxicity Platelet, WBC, GI and N&V. MRD 100-120 mg/m2/d x 5 or 45-50 mg/m2 po qd x 14 d. Prostate cancer: 5 d schedyule 31% PSA OR and 44% NC. SCLC: 38% PR (N=26); NSCLC No OR in 13 patients; Ovarian cancer: Similar to CDDP and CBDCA.

Ellipticine- Olivacine

Pyrazoloacridine. Intercalante, inhibe topo I y II, activo en celulas quiescentes, hipoxicas, y en celuklas que expresan MDR . MRD 150 mg/m2/d x 5. Toxicidad: hematologica, neurologica central (reaccion paranoide, ansiedad) Respuestas en cervix, ovario resistente, colorectal.

Enediynes

506 U

Penclomidine Oral (MTD 800 mg/m2 po x 5 d. DLT ataxia y confusion)
G Liu et al (Clin Ca Res 2002;8:706-11)

Sar-CNU

Bizelesine

Glufosfamide MTD 8000 mg/m2. MRD 5000 mg/m2 in 60 min iv q 3 wks (ASCO 2001)

BENDAMUSTINE
M Kalaycio (Cancer 2009;115:473-9). Bendamustine (TREANDA) in CLL/Low grade NHL. 120 mg/m2 d 1 & 2 q 3 wk iv or 90 mg/m2 d 1 & 2 q 3 wk for risk patients. Better than CBCIL in CLL (60% vs 30% OR). Bendamustine + RITX OR90%; MPFS 2y. Active after FLUDARA.

2.-Agentes interactivos con tubulina

Dolastatin, LU 103793. Peptido. Sensibilidad MDR altta MRD 3 mg/m2/dx5 q 3 sem. Toxicidad: neutropenia, hepatica, edemas

Rhizoxin Macrolido. MRD 1,2 mg/m2 civi 72 h. Toxicidad: Mucositis, leucopenia

Cryptophycin (LY 355708) Peptido. Baja sensibilidad aMDR. MRD 1,8 mg/m2 d 1&8 q 3 sem. Toxicidad: neurotoxico, mialgia, hipotension. Respuestas NSCLC

TAXANE ANALOGS

BMS 184476 Derivado mas hidrosoluble para eliminar la toxicidad del cremophor. MRD 60 mg/m2 q 3 sem. Actividad conservada y menor toxicidad en estudios de Fase I.

BMS 275183 (LE Broker et al, Clin Ca Res 2006;12:1760) Oral Taxane (4 methylcarbonate taxol analogue, MRD 5-20 mg/m2 wkly. N=48. DLT neuropathy, diarrhea, thrombocytopenia. OR 23.7% (NSCLC, sarcoma, prostate, PNET). MTD 200 mg/m2. Recommed Phase II in NSCLC.
Borker L et al (Clin Ca Res 2007;13:3906-12) BMS 275183, oral taxane. Phase I, MTD 100 mg/m2 biwk. OR 2 NSCLC, 2 prostate, 1 melanoma (N=38).

EK Rowinsy & E Calvo (Sem Oncol 2006;33:421-35). Interesting analogues:
Abraxane (ABI-007), nanoparticle albumin colloidal uspension, 300 mg/m2 q 3 wk, similar AUC, better distribution, higher tumor concentration and OR better than parent compound in randomized breast cancer trial. OR after TXL resistance.
CT 2103, polyglutamated paclitaxel with large trials in NSCLC (400 patients) less toxic 175 mg/m2 q 3 wk.
DHA-paclitaxel (chlorohexanoic, naturla fatty acid). 1100 mg/m2 q 3 wk
Oral formulations: DJ927, MAC 321.

S8184: Emulsion de Txl sin cremophor inhibe pgp. Estudios Fase I, a dosis 125-225 mg/m2 neutropenia, sin reacciones alergicas (AACR 2002, Abs2742)

Taxol
Omura GA et al (JCO 2003; 21:2843-8). HD Taxol randomized study associated to G-CSF no OS gain in spite of higher activity. Dose dense is preferred. Review of literature (JCO 2003;21:2810-4) confirmed no advantage found.

Taxotere
MN Fournier et al (Clin Ca Res 2007;13:5841-6). TXT 35 mg/m2 wkly followed by Flavopiridol 60-80 mg/m2 in 1 hr iv infusion. MTD not reached. OR observed in GEM resistant pancreatic cancer (1 CR (MDR>1y) and 1 PR; breast ca resistant to TXT and ovarian cancer amongst others… Active.
EG Chiorean et al (Clin Ca Res 2008;14:1131-7). N=25. TXT 30 mg/m2 wkly x 3 q

4 + Erlotinib 150 mg qd. OR observed in NSCLC, PC, HCC (1 CR). Toxicity neutropenia, skin, gastrointestinal.

A. Jimeno (Clin Ca Res 2009;15:3903-5). Eribulin mesylate (synthetic analog of Halochondrin B, microtubule modulator), Phase I MTD 2 mg/m2 q 3 wk or 1 mg/m2 wkly. Neutropenia, fatigue. OR: NSCLC, Endometrial, ovarian and TXT resistant breast cancer. (S. Goel et al, Clin Ca Res 2009;15:4207-12, wklu schedule) (AR Tan et al Clin Ca Res 2009,15:4213-9, q 3 wk schedule).

EPOTHILONES

BMS 247550 (drivative of EPOTHILONE B) activo despues de Taxanos en cancer de mama, cervix, melanoma, prostata.. (ASCO 2002, 410), cabeza y cuello, ovario, sarcoma (ASCO 2002, 412) 59 mg/m2 q 3 sem

S Goodin et al (JCO 2004:22:2015-25). Aza-epothilone B (BMS 247550) (Cremophor), requires antihistaminics, MRD 40-50 mg/m2 q 3 wk; hematological toxicity 50% neurotoxicity, fatigue, myalgia and emesis, with a 15% OR in breast cancer, 18% in NSCLC, and no responses in CRC. Epothilone B (BMS310705), water soluble, 40 mg/m2 q 3 wk, diarrhea. Epothilone (EPO 906) 6 mg/m2, DLT diarrhea, no hematological toxicity and OR 12% in TXN rsistant breast cancer, minor OR in CRC and 2/53 OR and 24/53 NC in RCC. Epothilone C (KOS 862), The best Pgp resistant of all epothilones studied in vitro, neurotoxicty, a hint of activity found in Phase I.

SM Gadgeel et al (Clin Ca Res 2005;11:6233-9). BMS 247550 (Epothilone B derivative) Phase I (N=17) MTD 40 mg/m2 q 3 wk. DLT 56 mg/m2 sepsis and ANC, emesis fatigue.

JJ Lee (Sem Oncol 2005;32:22-6). Epothilones evade MDR mechanism of resistance. Ixabepilone (BMSD 247550) Phase I 6 mg/m2/d; Phase II in breast cancer treated with TXn. N=37, OR 22% (23% CR + 19% PR + 35% NC, at 5 mg/m2/d x 5 q 3 wk; confirmed in 2 additional trials showing a 14% OR and 12% OR. Dose recommended 40 mg/m2. Phase III studies in breast cancer ongoing XEL+IXBP (expected 1200 patients).

E Rowinsky & E Calvo (Sem Oncol 2006;33:421-35). Interest because of activity was found in B-tubulin mutations, less dependency on Pgp, and activity shown in the same tumors that TXns. Ixabepilone is formulated in castor oil and leads to hypersensitivity reactions. Patupilone is active also in RCC and possibly in CRC. Epothilone D (Koss 862) less toxic compound. BMS 310705 is water soluble and produced diarrhea, showing activity in breast, ovary, urinary bladder, gastric and NSCLC.

L Gianni et al (JCO 2007;25:3389-91). Ixabepilone 6 mg/m2 qdx5 in 1 hr iv q 3 wk; 40 mg/m2 in 3 hr iv q 3 wk; 32 mg/m2 in3 hr in previously treated. Active in breast cancer (OR 20-57%) resistant to Anthracyclines, Txns and Xeloda. Active in NSCLC OR 15%. Neurotoxicity 30%; daily schedule is less neurotoxic, mild hematological toxicity.

R Plummer et al (Clin Ca Res 2008;14:8288-94). Phase II CBDCA AUC 5-6 + IXBP 40 mg/m2 q 3 wk or 25 mg/m2 d 1&8 q 3 wk (less neurotoxic). N=52. OR 12%; breast, neuroendocrine, mesothelioma, adenocarcinoma unknown primary.

S Faivre et al (Eur J Cancer 2008;44:674-82). N=41. IXBP 15-30 mg/m2 + CPT 120-180 mg/m2 q 3 wk. MRD IXBP 20 mg/m2 + CPT 180 mg/m2 q 2 wk. OR: 5 (4 in NSCLC and 1 in SCC unknown primary).

VINCA DERIVATIVES

VINFLUMINE (VFL) (L0070) is a bifluorinated vinca derivative, active in resistant cell lines to vinca. MTD 400 mg/m2 q 3 wk (hematotoxicity and neurotoxicity), MRD 350 mg/m2 q 3 wk (AACR 2001) (4478)

J Bennouna et al (Clin Ca Res 2008;14:1625-32). Vinflumine better in xenografts when compared to Vinorelbine. MRD 320 mg/m2 q 3 wk. Less neurotoxicity and hematologic, fatigue & constipation profile. Phase I: 350 mg/m2 q 3 wk; 120-150 mg/m2 wkly; 170 mg/m2 d 1 & 8 q 3 wk. Phase II/III: Urinary bladder failure to prior Pt derivative 18% OR; Breast cancer after TXn/ Anthracycline OR 30%; NSCLC 8% OR after Pt derivative and Phase III equal to TXT; Mesothelioma 14% OR (N=62); No activity in melanoma, CRC, RCC and ovary cancer.

Vinorelbine:
E. Briasoulis et al (Clin Ca Res 2009;15:6454-61). Metronomic NVB tiwk. MTD 50 mg. OR 8% PR and 32% NC>6mo. OR > 3y observed in RCC, medullary thyroid, Kaposi

3.-Agentes antimetabolitos y análogos

Inhibidores de la TS: AG 331
Thymitaq

Inhibidores de las purinas: Peldesine
506U78 (Pro-Ara-C)

Inhibidores de la DHPDH:
5-Ethyniluracil 10 mg/d + 5FU 1 mg/d x 14-28 d q 5 sem.
S-1: 5FU prodrug Tegafur + 5 chloro 2,4 dihydroxypyridine + K-oxonate (1:0.4:1 Molar). Administracion MRD 40 mg/m2 q 12h x 28 d q 5 sem.
Toxicidad: Diarrea. Activo.
5FU CIVI> po 5FU+Eniluracil, steady state and AUC better (x3!!!) (ASCO 2001)

JL Green (Clin Ca Res 2005;11:5067-8). Complete DPD deficiency 0.1% population and relative deficiency in 3-5% population. DDP measurement is labor intensive and 2-^{13}C uracil breath test discriminates very efficiently (Mattison LK et al Clin Ca Res 2005;10:2652-8).
*********Mattison LK et al (Clin Ca Res 2006; 1:549-55) 2-^{13}C Uracil breath test (UraBT) for DPD defiency 96% specificity and 100% sensitivity. In 31 volunteers: 19 normal, 11 partial DPD deficiency and 1 profound deficiency.**

Antimetabolites:
Troxacitabine (BCH 4556) Análogo configuracion L-nucleosido (todos los utilizados son dextro, incluidos todos los naturales) resistente a la deaminacion y conduce a terminar la cadena DNA. MRD 10 mg/m2. Toxicidad:
Rash, sindrome mano-pie. Eliminación renal. Respuestas en leucemias, renal y NSCLC.

CAFdA Análogo fluorinado de cladribina con mayor retencion y mas eficacia como sustrato de deoxycytidine kinase. Interesante

Ara-C Depot 25-50 muy activo en ALL: 4/9 CR en resistentes a los 8 dias. Recomiendan 35 mg intreventricular (ASCO 2002, Abs433).

B Cole et al (Cancer 2003;97:3053-60). N=61, meningeal carcinomatosis. Randomized <u>IT Depocyte, 50 mg x 6</u> in 3 months (OR 26%, MST 105c) vs it <u>MTX 10 mg x 16</u> in 3 months (OR 20%, MST 78 d), indicating similar activity, less toxicity and longer TTP for Depocyte. Also benefit of less demanding dose schedule.

************J Braess et al (Clin Ca Res 2005;11:7415-25). Studied AraC and found that total dose and AUC were not sensitive for activity and toxicity. Then developed a model based on Concentration/Exposure times/ and correlated with toxicity. C^N x T, which incorporates N and proved to be a constant value for AraC. AraC, N=0.45, proved to be quite sensitive in 49 study arms with a tiotal of >10.000**

patients. Topotecan N=0.45; Dauno N=071; IDA N=0.78; MTZ N=0.72; VP N=0.78 nad Mafosfamide N=3.71. AraC is easy to model because reaches steady state concentrations very soon and t½ά is 6-7 min, t½ß 2-3 h, quite fast so that infusion time correlates with concentration time. Enough protocolos have indicated toxicity. These results indicate that protocols can be optimized and modelin is very interesting for drugs with a N value far from unity to gain activity.

Gemcitabine: La tasa de respuesta es idéntica para la pauta de 1g/m2/sem x3 q 4 sem y 90 mg/m2 dos a la sem x 3 q 4 sem en NSCLC (19-22% RO). Impacto economico!. La dosis de saturación enzimatica dFdCTP intracelular se consigue con GEM 10 mg/m2/min (15-20 umol/l). GEM activity is reduced by the concomitant use of Dexamethasone (AACR 2001) (435)
GEM civi 96 horas: 35 mg/m2 dosis total (MTD). (ASCO 2002, Abs 2137)

*******M. Tempero et al (JCO 2003;21:3402-8). N=92, pancreas cancer. Randomized GEM Fixed dose rate 10 mg/m2/min (1500 mg/m2 in 150 min (MOS 8 mo, MST 7.3 mo, 2 yOS 18.3%) vs GEM 2.2 g/m2 in 30 min (MOS 5 mo, MST 4.9 mo, and 2 yOS 2.2%).**

E Sugiyama et al (JCO 2007;25:32-42). Cytidine kinase polymorphism 208G>A (Ala to Thr) decreased clearance of GEM in Japanese patients with excess neutropenia when administered combined to CDDP or 5FU.

J Matsubara et al (JCO 2009;27:2261-8). Severe ANC and thrombocytopenia after GEM correlated with low haptoglobin (by tamdem mass spectrometry).

Antifolatos:
Edatrexate MRD 80 mg/m2. Activo en NSCLC, cabeza y cuello.

Premetrexed. Alimta (LY 231514 (MTA) inhibe TS, DHFR y glicinamide ribonucleotide formyltransferase. Activo con Ro>20% en primera linea en NSCLC, mama, colon, vejiga, cabeza y cuello, cervix. Toxicidad: hemaologica, hepática, rash, no alopecia. DLT: neutropenia y digestiva. MTD 4 mg/m2/d x 5 q 3 sem; 40 mg/m2 sem x 4 q 6 sem; 600 mg/m2 q 3sem. Actividad en Fase II: colorectal 17%, cabeza y cuello 35%, pancreas 6%, vejiga urinaria 35%, NSCLC 35%, mesotelioma 40%, mama. Ser puede combinar sin incremento de toxicidad con RT y QT. (Sem Oncol 2002;29:8-16)

F Fosella, U Gatzmeier (Sem Oncol 2002;29:8-16). Premetrexed best schedule q 3 wk, MTD 600 mg/m2 in 10 min infusion, less toxic than wkly or daily schedule. Given together with FA (5 mg qd starting 2 days before) and Vit B12 (1000 ug im 1-2 wks before and repeated q 9 wks) can be increased up to a dose 1200-1400 mg/m2 q 3 wk. Given with both Vits can be given at full doses with CPT, GEM, CDDP, CBDCA, LOHP, 5FU, TXT, NVB, TXL, & RT. Side effects hemaotlogical, GI, rash. OR in CRC, pancreas, NSCL, mesothelioma, Bladder, cervix, H&N.

4.- Inhibidores de la topoisomerasa I

Topotecan

Topotecan capsules (Hycamtin) 2.3 mg/m2/d x 5 d q 3 wk (approved SCLC)

DS Boss et al (Clin Ca Res 2009; 15:4475-83) Combination study. N=43. CBDCA AUC 4 d 3 + TPTC 0.5 mg/m2/d 1-3 q 4 wk. Thrombopenia. T→ C better than C→ T because it is less toxic. OR: 1 CR SCLC + 5 PR ovary, SCLC, gastric + 21 NC

JR Molina et al (Clin Ca Res 2008;14:7900-8). N=37. Combination Lapatinib 1250 mg/d qd + TPTC 3.2 mg/m2 d 1, 8 & 15 q 4 wks. Fatigue, N&V, diarrhea. NC=46%.

Irinotecan

R Mathijssen et al (JNCI 2004;96:1585-92). Cytochrome P450-3A4 phenotype predict PK of CPT11. CYP P3A4 phenothype compared very similar with erythromycin metabolism & midazolam clearance, showing a good correlation with CPT clerance. Phenotype UGT1A1 related to increased exposure to SN-38 (homozygous 435ng.h/ml and heterozygous 631 ng.h/ml.
F Innocenti et al (JCO 2004;22:1382-8). UGT1A1 genotype and total bilirubin identify severe CPT toxicity. UGT1A1 responsuible of SN-38 glucuronidation, inactivating active metabolite.
******MJ Ratain (Clin Ca Res 2006;12:1658-60). UGT1A1*28 polymorphisms studied when giving CPT 350 mg/m2. Identified correctly 6/6 TA repeats non toxic, 6/7 intermediate and 7/7 quite toxic with 50% grade IV ANC.**
*******Han et al (JCO 2006;24:2237-44). UGT1A1*28 polymorphism identified increased tocxicity in occidental patients and UGT1A1*6 polymnorphism identified increased toxicity in oriental patients. Make a 20% dose adjustement.**
*******LJ Schaaf et al (Clin Ca Res 2006;12:3782-91).Phase >I study in patients with impaired liver function. N=42. Group I: TB 1.5-3xN, ALT/AST <5-5xN had a MTD 60 mg/m2; Group II: TB 3.1-5-3xN, ALT/AST <5-5xN had a MTD 50 mg/m2; Group III: TB <1.5xN, ALT/AST 5.1-20xN had a MTD 60 mg/m2; Group IV: TB 1.5-3xN, ALT/AST 5.1-20xN had a MTD 40 mg/m2.**
DL Kroetz (JCO 2008;24:4225-7). CPT activity depends on UGT1A1 which mediates conversion to active SN38-SN38G metabolites and also of the activity of disposition enzymes PgP-ABCB1, MRP1-ABCC1, MRP2-ABCC2 and MXR-ABCG2. Higher toxicity can be due to the presence of UGT1A1+28 7/7 TA repeats instead of 6/6 TA repeats and also lowwer expresion of PgP-MRP2, both increasing systemic exposure to SN38.
**********J Hoskins et al (JNCI 2007;99:1290-5). Metanalysis of 10 series with N=821.UGT1A1 28*/28* genotype associated with toxicity at medium and high doses of CPT (OR= 3.2 and OR=27.8, respectively), but not with low dose CPT (OR=1.8). Commonly used CPT doses in the range of 100-125 mg/m2 are too low for increased toxicity.**
*****J Hoskins et al (Clin Ca Res 2008;14:1788-96).TOP1 related to neutropenia and response in CRC treated with CPT. XRCC1 haplotype CGGCC-G had best OR (83% vs 30%).**
J Deeker et al (cancer 2008;113:1502-10). UGT1A1*28 predicts hematological tocxicity and diarrhea for high dose CPT together with other factors: bilirubin, age, sex.

F Innocenti et al (JCO 2009;27:2604-14). Composite pharmacogenomics for CPT include UGT1A1*28, UGT1A1*93, ABCC1, SLOC1B1*1b and contribute >50% variation in the ANC nadir/AUC.

DX 8951f (Exatecan mesylate). MRD 0,4 mg/m2/d x 5 q 3 sem. ; 2,4 mg/m2 activo en CRC resistente a CPT-11+5FU, SCLC, próstata, timoma. Toxicidad hematológica. Need of measuring AUC of TPT to target dose ranges (ASCO 2000, 732).
BN 80915, stable camptothecin, orally available MTD 0.27 mg, activity shown (ASCO 2001)
BMS 251873 (fluoroindolocarbazole) inhibitor of Topo I> CPT in prostate cell lines (AACR 2001).

D Soepenberg et al (Clin Ca Res 2005;11:703-11). Phase I DE-310 prodrug of exatecan, 1-2 mg/m2, 3 h iv q 2 wk ; 6-9 mg/m2 q 6 wk. Terminal half life 2 wk!!... programmed to be repeated q 6 wk. N=27, Toxicity hematological (N, Plat) and VOD of the liver. OR: 1 CR adenocarcinoma, 1 PR pancreas, 14 NC. MRD: 7.5 mg/m2 q 6 wks.
G Batist et al (Clin Ca Res 2009; 15:692-700). CPX1-Liposome (Irinotecan + Floxuridine) 1 unit= 1 mg CPT + 0.36 mg Floxuridine, Phase I. MTD 210 Units/m2. Toxicity diarrhea 24%, ANC 12%, hypopotasemia 12%. PR 12% (3/25). IN CRC 13% OR resistant to CPT.

A Zhou et al (Clin Ca Res 2009;15:374-81). Phase I Gimatecan. N=33. MTD 2.4 mg/m2 wkly po (lipophilic), terminal ½ά 77 ± 37 h.

Karenitecin, 1 mg/m2/d x5 q 3 sem. Activo en tumores SNC en niños (2/7 OR) (AACR 2002, Abs 2748)

DNA REPAIR INHIBITORS

C Calabrese et al (JNCI 2004;96:56-67). PARP inhibitor AG-14361, MTD 1 g/m2 wkly. Toxicity mild hematological, N&V, fatigue. Minimal reponse observed (8/34). Recommend to combine with TMZ and other DNA damaging drugs.

K Ratman et al (Clin Ca Res 2007;13:1383-8). PARP (PolyADP-Ribose Polymerase) binds to DNA breaks and recruits other proteins for DNA repair. Inhitors of PARP are small molecules non toxic and potentiate chemotherapy effect. Current on going trials with AGO-14699 associated to TMZ, KU 59436, ABT 888 oral, BSI-210, INO 1001 associated to TMZ, GPI-21016…

ER Plummer, H Calvert (Clin Ca Res 2007;13:6252-6). PARP 1 and 2 homologs are active in base excision repair and single strand breaks. Inhibitors of PARP potentiate alkylating agents and RT damage. BRCA1 and BRCA2 deficient cells show exquisite sensitivity to PARP inhibitors. This can be used in synthetic lethality approaches because of a defective DNA repair cancer cell.

S Kummer et al (JCO 2009;26:3785-90). ABT 888 po 10-50 mg inhibited PARP, and could be used clinically in combination with DNA damaging agents…

5.-Inhibidores de la angiogenesis

TNP470. Inhibidor de celulas endoteliales MRD 60 mg/m2 infusion iv 1 h tres a la sem. Respuestas en cancer renal. Toxicidad vértigo, mareo, ataxia, confusión, ansiedad, todas reversibles.
TNP470 (antiangiogenesis) MTD 20 mg/m2, double dose required for antiangiogenic effect (ASCO 2000)

Tetrathiomolibdate. Inductor de deficiencia en Cobre. Se utiliza la ceruloplasmina serica como marcador de, buscando la reducción de 20% sin que baje el hematocrito >80% del basal. TM, 120 mg/d lo consigue en 75% de casos y después se mantiene en estos limites. Estabilización tumoral demostrada en algunos pacientes. TM se ha desarrollado para el tratamiento de la enfermedad de Wilson.
Tetrahydromolibdate (chelator of Cooper) proven safe for human therapy. (ASCO 2001)

S Lowndes et al (Clin Ca Res 2008;14:7526-34). Cooper chelation ATN224 (second generation analogue of ammonium tetrathiomolybdate). Ceruloplasmin reduction from 16-60 mg/dL normal values to 5-15 mg/dL in 14-21 d. N=18. MTD 330 mg/d. Toxicity: Fatigue grade 3, anemia, ANC, sulfur eructation. Target cerulaplasmin acheieved at d 21. Reduction of RBC superoxide dismutase 1 activity >90% and then maintenance therapy 90-150 mg/d (titrated) together with omeprazol.

Endostatin. Actualmente escalando la dosis a 600 mg/m2 en 20 min infusión iv. Por PET y TAC se ve disminución de vascularizacion. Resopuestas minor en melanoma.
rhu Endostatin, Phase I, up to 600 mg/m2. Activity shown in melanoma, synovial sarcoma (ASCO 2001, 9)

rhu Angiostatin, Phase I, up to 120 mg/m2. Urine VEGF decrease 64-70% (ASCO 2001, 10).
Angiostatin 7,5-15 mg/m2 subcutaneo bid (ASCO 2001, 322)

Neovastat (AE941) 240 mg/bid. Fase II en renal, MST 16,3 m, 2 PR, 2yOS 36%. No efecto a dosis 60 mg/bid (ASCO 2002, Abs1907)

SU 5416. Inhibidor de Flk-1/KDR de VEGF. MRD 145 mg/m2 iv en 1 h infusión. Toxicidad: nauseas, vomitos, diarrea, astenia, cefalea. Respuesta en Sarcoma de Kaposi (alguna RC!). Actualmene en estudio SU 6668, análogo de efecto mas amplio.

Thalidomida Multiples acciones: inhibicion de señales (IL6, bFGF, VEGF, TNFalfa), induce respuesta proliferativa en T8, modula moleculas de adhesion, supresion de COX2.

DMXAA, derivative of flavone acetic acid, inhibe la circulacion durante 24 h (JCO 2002; 20:3826-40)

LENALIDOMIDE
A List (NEJM 2007;357:2183-6). Lenalidomide (Revlimid, CC5013 and Actimid, CC4047). Inhibits angiogenesis, cell interaction (IL6, TNFa), proliferation (apoptosis), cell adhesion (VCAM, selectins) and stimulate T cell, IL2, IFNg, NK, cytotoxicity.

Tecogalan

Neovastat AE-941, complex of natural cartilage antiangiogenic factors is now in Phase III due to some survival gain in NSCLC and renal cell cancer (AACR 2001) (2916)

BEVACIZUMAB
J Gandreault et al (Ann Oncol 2004;15:329P). PK of BV q 2 wk 5 mg/kg vs 7.5 mg/kg q 2 wk no differences; also 10 mg/kg q 2 wk vs 15 mg/kg q 3 wk no differences.

G Semenza (NEJM 2008;358:2066-7). PIGF (Placental growth factor antibody) binds VEGFR1 which target only pathological vessels without inhibition of macrophages and for this reason avoids resistance to anti-VEGF therapy. BV binds VEGFR2. Combination of PIGF and BV results in better inhibition and probably inhibit vascular and lymphatic vessels (Fisher et al, Cell 2007;131:463-75).

V Eremina et al (NEJM 2008;358:1129-36). Early effects of antiVEGF are the inhibition of podocyte secretion of VEGF and mesangial/glomerular endothelial cells causing thrombotic nicroangiopathy (clinically relevant proteinuria initially and hypertension secondarily). Withholding BV makes renal impairment reversible. Elegant traial ad knockout mice proving this mechanism of hypertension due to BV.

**************L Ellis and D Reardon (Nature 2009;458:290-2). (M Paez Ribes et al, Cancer Cell 2009;15:220-31; Eboson et al, Cancer Cell 2009;15:232-9). BV single drug after chemotherapy do not induce tumor dormancy but stimulate cell changes towards invasive phenotype with more metatasis. Wait the results of maintenance trial of CRC. GBM showed increase in distant mets confirming the results of a previous mouse model.**

M Mazzone et al (Cell 2009;136:839-51). Prolyl hydroxylase domain 2 (PHD2) is oxygen sensor that tags hypoxic induced transcription factors. Haplodeficiency of

PHD2 normalize endothelial tumor cells, improve drug delivery and oxygenation, decrease metastases and prolong surivial. Use of antiangiogenesis drugs produce normalization for 1-3 wks, a good time window for chemotherapy. Recommend to combine antiPHD2 with chemotherapy (RK Jain, NEJM 2009;360:2669-71).

PAZOPANIB
H Hurwitz et al (Clin Ca Res 2009; 15:4220-7). Phase I GW786034, oral angiogenesis inhibitor, VEGFR, PDGFR, cKIT. N=63. MRD 800 mg po qd or 300 mg bid po. Results: 3 PR and 14 NC>6mo.

VASCULAR DISRUPTING AGENTS
WJ Van Heckeren et al (JCO 2006;24:1485-8). Vascular disrupting agents: ZD6126, Combretastatin A4 Phosphate, TZT1027, AVE8062, ABT751, MN029, exherin & 5,6 dimethylxanthenone 4 acetic acid. Cause elevation of cardiac troponin (CPK-MB fraction, >10 u/L indicate severe myocardial necrosis), PTE, elevation of IL6 prior to necrosis, circulating endothelial or progenitor endothelial cells from BM, cause tumor necrosis and decrease tumor blood flow (up to 80%), and show clearly this effect in the MRI-dynamic contrast enhanced study(DCE-MRI). Requires new toxicology…!

Combrestatin A4. Toxicidad vascular con reducción de 93% de circulación sanguínea a las 6 horas. MRD 60 mg/m2 infusion de 10 min q 3 sem. Respuesta completa en carcinoma anaplasico de tiroides mantenida >1 año sin tratamiento!!. Toxicidad: nauseas, vomitos, dolor en tumor y flush.facial. Sindrome coronario agudo en dos casos, dolor tumoral en 10%

Combretastatin A4 68 mg/m2 in 10 min iv wkly x 3 q 4 shows good tolerance and reduction of blood flow (ASCO 2001)

ZD6126
L Beerepoot et al (JCO 2006;24:1491-8). N=32 solid tumors. ZD6126 Phase I: Dose range 5-28 mg/m2 wkly; t½ alpha 1-3 hr linear disposition with dose. At 10 mg/m2 1 patient had AMI 2 wk later and 4 had elevation phosphokinase muscle brain elevation. MTD 20 mg/m2. DLT: hypoxia due to TEP and decrease in LV ejection fraction. Circulating endothelial cells found after infusion. No OR observed.

6.-INHIBIDORES DE INVASION Y METASTASIS

CAI (Carboxyamidotriazole)

FB642 (carboxyimidazole analogue), po wkly up to 19.2 g/m2/wk: MR 1 ovary, 1 renal, 1 leiomyosarc/26 pts (ASCO 2000)

PI-88. Inhibidor de heparanasa

Inhibidores de metaloproteinasas

J Arribas (NEJM 2005;352:2020-1). MMP-1 binds PAR-1. When anti MMP-1 are given, block of PAR-1 is released and G-protein activate And regulate tumor invasion factors. MMP-1 inhibitors do not work clinically because other small peptides do the same effect than MMP-1. Suggests that PAR-1 inhibitors are a better target

Marimastat: Via oral 25-75 mg bid x 4 sem. Solo hay un estudio positivo randomizado en gastrico (Proc ASCO 2000:19:240). Resto de estudios no concluyentes,inferiores o iguales a quimioterapia.

Batimastat. Mala absorcion. No se estudia ya.

Bay 12-9566 . Se han suspendido todos los estudios randomizados por inactivo.

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BMS 275291

CGS 27023ª: RD 300 mg bid. Rash y alter musculoesqueleticas

AG 3340, 10-35 mg po qd, respuesta en melanoma y NSCLC

BMS-275291. N Rizvi et al (Clin Ca Res 2004;10:1963-7). BMS 275291. Oral nonhydroxamate sheddase sparing MMP inhibitor given po. MRD Phase I: 1200 mg/d. No associated osteomuscular toxicity as the original compounds.

COL-3. MRD 36 mg/m2/d. A dosis altas da fototoxicidad, anemia, estreñimiento y neurotoxicidad. Activo en Sarc Kaposi: OR 44%, MDR 25+sem.

BJ Dezube et al (JCO 2006;24:1389-94). N=75 . COL-3 (metalloproteinase inhibitor) showing benefit in AIDS related Kaposi sarcoma. Randomized COL-3 50 mg qd po (41% OR, benefit 78%& 3 CR) vs 100 mg po qd (26% OR, 63% benefit, MDR > 1y. Toxicity photosensitivity and rash. Indication of reduction in klevels of MM=2 and MMP9.

Inhibidores de integrinas

R Stupp et al (JCO 2007;25:1637-8). Integrin inhibitors cause regulation of cell

adhesion, proliferation, survival and migration. Cilengitide (αVβ3 and αVβ5 receptor binding) Phase I in glioma. MRD 2400 mg/m2 biwk; no DLT found. Activity: 5 PR + 16 NC out of 51 patients (Nabose, JCO 2007;25:1651-7).

7.- Agentes moduladores del control del ciclo celular y señales

Editorial JNCI 2005;97:1026-7). New cell cycle checkpoints blockers are ready for clinical trials. Two check points: ATM-chk2 is the first at boundary G1-S and becames spoiled through p53m Rb, p21, & p16 alterations in many tumors, causing the cells to move to synthesis phase and have only the second checkpoint to stop and repair damaged DNA. The pathway second checkpoint is ATR-chk1 at G2-M boundary. If cells are not stopped here they proceed to death. New compounds are ready CBP501(CanBas) and XL844 (Exelixis). Older compounds were only modestly effective (Rapamycinm UCN-01, 17-AAG). If the new compounds are really effective probably they would generate and excess of new tumors.

G Powis et al (Clin Ca Res 2006; 12:2964-6). PI3K-AKT is the signaling pathway most frequently mutated/overexpressed in cancer due to the activation of growth factors, integrins, PTEN loss and Ras. Drugs: pi3K inhibitors (PX866, SF1126, IC4-86068, ZSTK 474), AKT inhibitors (PX316, Perifosine, UCN-01), PDK 1 inhibitors (OSH 030P2), m-TOR inhibitors, growth factor receptor inhibitors, ras inhibitors, etc…

RO 31-7453

Safingol IC 50=33uM. Respuestas en sarcoma y páncreas.

E7070 analogo de chloroquinoxaline sulfonamide, inhibidor de CDK. RD 600 mg/m2 iv q 3 sem. Toxicidad: alopecia, hematologica, acne, mucositis, fatiga.

Flavopiridol

(Transicion G1-G2) IC50 a 66uM. Inhibe cdk, ciclina D1 e induce apoptosis. MRD 50 mg/m2/dx3 en infusión continua (civi). Respuestas en renal, NHL, CRC y gástrico. Sinergismo con TXL (respuestas en asociación a TXL en esófago resistente a TXL), y con CPT-11. DLT diarrea.
Flavopiridol after TXL and simult with CDDP: TXL 175 mg/m2 and 24 h later CDDP 50 mg/m2 + Flavopiridol 80 mg/m2 (MTD), found some response in resistant NSCLC and esophagus (AACR 2001) (2917)

GI Shapiro et al (JCO 2006;24:1770-83). Flavopiridol inhibits cdk4, 6, 2, 1 and causes Rb dependent G1 arrest. A 24-72 hr infusion had no effect on CLL or MCL while a 30 min infusion followed by 4 hr infusion induced a 41% OR and tumor lysis in MCL. AG024322 also is a pan cdk inhibitor. Seliciclib inhibits cdk2,1 (BMS 387032, NU 6102). PD 0332991 inhibits cdk4/6, theoretically recruiting S-Phase cells with chemotherapy can enhance their activity. Cdk inhibition do not have antiproliferative effect, but occasionally leads to apoptosis.

PROTEIN KINASE C INHIBITORS

Bryostatin-1 (Protein kinase C)MRD 120 ug/m2 en 72 h infusión continua q 2 sem. Respuesta en melanoma, ovario y LNH. Toxicidad: Mialgia, cefalea, flebitis, reaccion aguda.

UCN-01 Staurosposine

Ca dependent PKC with Ic 50 a 30 nM. Vida media muy prolongada, >30 dias. MRD 42,5 mg/m2/dx3.Toxicidad: Nausea, vomitos, hyperglucemia, hipoxemia. DLT 42,5 mg/m2/dx3. Respuestas: leiomiosarcoma, melanoma, NHL.

RP Perez et al (Clin Ca Res 2006;12:7079-85). UCN-01 (NSC 638850), chk 1 inhibitor 22 hr after CDDP 3 days civi q 4 wks. MTD CDDP 30 mg/m2 → UCN-01 34 mg/m2/d x 3 civi q 4 wksa. When CDDP was given at 40 mg/m2 or UCN-01 was fiven at 45 mg/m2 day caused heart toxicity, CNS hemorraghe, fibrillation, MI, hypoxia).

JM Rademaker-Lakhai et al (Clin Ca Res 2007;13:4474-81). Phase I Enzastaurin PKC inhibitor and pI3K/AKT inhibitor. First alone 350 mg-500 mg po x 14 d and then q 3 wk associated to GEM 1000-1250/m2 d 1&8 + CDDP 60-75 mg/m2 d 1 &8. N=33- Toxicity QT prolongation, fatigue, nuetropenia, thrmbopenia. OR: 3PR (pancreas, ovary and H&N) + 13 NC. MRD Enzastaurin 500 mg qd.

B Teicher et al (Clin Ca Res 2006;12:5336-45). PKC family interact with multiple SK-TK regulating proliferation, gene expression, cell cycle, differentiation, cytoskeletal organization, cell migration and apoptosis. Involved mechanisms proven in cncer of the skin, CRC, gastric, prostate, ovarian, breast, endometrial, lung, gliomas, myeloma, leukemias and lymphomas. Among the PKC inhibitors: UCN-01 (staurosporine), PKC-412 (Midostaurin,, also a TKI); LY-317615 (Enzastourin (also VEGF and PKCbeta inhibitor, actually in Phase II in glioma compared to BCNU and in NHL as a maintenance after chemotherapy.

M Carducci et al (JCO2006;24:4092-9). Phase II Enzastaurin. N=47. No MTD up to 700 mg/d. MRD 525 mg qd. Side effects: Fatigue, GI, chromaturia. Results: N=20, NC.

M Serova et al (Sem Oncol 2006;33:466-78). PKC >12 isoenzymes, involved in signal transduction (RAF, MEK, ERK, IKK, NFkB, antiapoptosis). Agents: Phorbol esters (Phorbol 12 myristate 13 acetate); Bryostatins (not in Phase III, disappointing results in Phase II); Antiestrogens (TMX); Staurosporine derivatives, bisindol maleimides (UCN-01); calphostins; & antisense ON (ISIS-3521, in combination with ChX in NSCLC gave 48% OR and 2% CR.

AURORA KINASE AND POLO-LIKE KINASE INHIBITORS

O Gantschi et al (Clin Ca Res 2008;14:1639-48). Serine-threonine Ki-Aurora Ki A, B & C are expressed during cell cycle and mitosis. Overexpression, amplification and polymorphisms correllate with aggressive histology and genetic instability. Inhibitors: MK 0457 (AURKA1, AURKB, FLT3, BCR-ABL, T315I, JAK) shown some OR in AL: AZD 1152 (NC in solid tumors); PHA 739358.

A Jimeno et al (JCO 2008;26:5504-10). ON-0191.Na (Poli-like ki 1 inhibitor, cause cell cycle arrest in G2/M. N=20. MRD 3.120 g in 2 hr iv d 1, 4 , 8, 11, 15, & 18 q 4 wk. Toxicity skeletal, abdominal, tumor pain, nauseas, fatigue, mild hematological. OR: 1 CR in ovarian cancer.

K Mross et al (JCO 2008;26:5511-7). Bi 2536 (Polo-like ki1 inhibitor). N=40. Phase I. MTD 200 mg/m2. Reversible neutropenia 56%, N&V, fatigue, anorexia.

M-TOR inhibitors & RAPAMYCIN ANALOGUES

TEMSIROLIMUS. CCI-779. No toxicidad hasta 60 mg/m2. Respuestas 2 renales y neuroendocrino, cervix, sarcoma, próstata, mama. Toxicidad: escasa, alteraciones ungueales, eccema, distrofia cutánea. Absorción oral.

J Peralba et al (Clin Ca Res 2003;9:2887-92). CCI-779 PK correlated with inhibition of p70s6 kinase activity in PBMNC on a wide dose range 25-250 mg iv lasting >72hr. The 25 mg dose wkly is optimal. Mild toxicity.

J Dutcher (Clin Ca Res 2004;10:6382-7). Phase II in RCC. N=110. Dose range 25-250 mg/m2 wkly, MRD 25 mg/m2. OR 7%, benefit 51%.
S Chan et al (JCO 2005;23:5314-22). CCI-779 75 mg or 250 mg iv q wk. Phase II in breats cancer: OR 9.2% (10 PR/109) Toxicity: depression 3-4 in 10%, mucositis 70%, rash 51%, N&V 43%, leukopenia 7%, hyperglycemia, somnolence, thrombopenia.
********T Witzig et al (JCO 2005;23:5347-56). Phase II MCL t(11;14). OR 38% (13/34); MTTP 6.5 mo, MDR 6.9 mo.**

E Galanis et al (JCO 2005;23:5294-304). Phase II glioma. 250 mg q wk.Response T1, Flair & gadolinium uptake 38%.

M Hidalgo et al (Clin Ca Res 2006;12:5755-67). CCI-779 (Temsirolimus, Torisel) iv qd x 5 q 2 wk. Phase I: 15 mg/m2/d (MTD) for minimal prior therapy and 9 mg/m2/ for new patients. N=63, asthenia, mucositis, N&V, cutaneous. Terminal half life 13-25 h. Results: 4 PR + 2 NC.

B Rini (Clin Ca Res 2008;14:1286-90). Temsirolimus active in PTEN altered tumors. MRD 50 mg wkly. Active in breast ca (N=35, OR 9%); GBM (36% improvement), amntle cell lymphoma (OR 38%, N=35), RCC (7-9% OR), neuroendocrine tumors (improvement 36%).

J Tabernero et al (JCO 2008;26:1603-10). Everolimus, Phase I 10 mg qd or 50 mg wkly. N=55. Benefit 4 aptients (1 PR in CRC). Toxicity sinusitis, neutropenia, hyperglycemia.

A Jimeno et al (JCO 2008;26:4172-9). N=21. Sirolimus 2-9 mg qd. MTD 6 mg qd po. Toxicity: 20%, hyperglycemia, hyperlipidemia, trasnaminitis, anemia, alopecia, WBC, neutrophil, mucositis.

A. O`Donnell et al (JCO 2008;26:1588-95). Everolimus Phase I. MRD 20 mg wk. S6KI inhibited 7 d at 20 mg/wk. Results: 5/10 RCC NC and 4 PR.

C Tanaka et al (JCO 2008;26:1596-602). Everolimus (RAD-001). S6KI inhibitor. MRD 20-30 mg wkly.

M Mita et al (JCO 2008;26:361-7). Deforolimus (AP 23573, MK 8669) m-TOR inhibitor. Phase I iv qd x 5 q 2 wk. MTD 18.75 mg/d. Toxicity: Mouth sore, rash. PR in NSCLC, RCC, ES, Mullerian mixed tumor and NHL. Decrease in p4E-BPI confirmed.

F Meric-Berstann & AM Gonzalez Angulo (JCO 2009;27:2278-87). M-TOR signaling targets: Mantle cell lymphoma (OR 25%) showing Cyyclin D1 overexpression, RCC, endometrial cancer, sarcomas (activation IGF1R) and Glioma. Drugs: Temsirolimus 25 mg iv wkly, Everolimus 10 mg po qd, Deforolimus 12.5 mg x 5 d q 2 wk. Markers of effect S6K1 and 4E-BPI, Combination with IGF1R inhibitors, chemotherapy, octreotide and trastuzumab or antiestrogens are synergistic. New m-TOR analogues target mTORC1 and mTORC2 (AKT) in a distinct way.

JK Garber (JNCI 2009;101:288-90). mTOR inhibitors lead to Akt upregulation (negative feedback loop disruption). All approved mTOR inhibitors inhibit TORC1 (Rapamycin analogs) and current developments are working on TORC1 and TORC2 inhibitors as well (OSI-027, KU0063794). Expected synergies are: inhibition of mTOR and IGF1R, combination mTOR inhibitor and chemotherapy, combination mTOR and MAPK or mTOR and PI3K.

8.- MODULADORES DE LA EXPRESION DE ONCOGENES

Dendrogram showing TKI specifity for different drugs

8.-Moduladores de la expresion de oncogenes

S Sharma et al (Clin Ca Res 2006;12:4392s-5s). Oncogenic addiction (IB Weinstein, Science 2002;297:63-4) applies to tumor cells presenting with multiple genetic alterations when they are dependent on a single oncogenic activity for their survival and has been observed in multiple models and also in response to Gleevec and Iressa). This concept can be used in synthetic lethal approaches. Oncogenic shock applies (as referred by DA Haber) to an alternative hypothesis to explain the effect found when signal attenuation of prosurvival balance by treating an oncogene, leads to temporary exceso of proapoptotic signals causing cell death. Implications are synergism of downstream prosurvival inhibitors but antagonism for apoptotic inhibitors.

Inhibidores de la farnesylyransferase:

R 115777 MRD 500 mg/m2 bidx5d q 2 sem. Toxicidad: nausea, vomitos, minima hematologica. Respuesta: CRC, Leucemia mieloide aguda y mama(3RP+9NC/27 pacientes).
L 744832
SCH 66336 DLT 400 mg/m2 bidx7 q 3 sem. Via oral. Toxicidad digestiva, diarrea. Respuesta en NSCLC

FTIs:

BM214662 Phase I with single agents (in combination) (ASCO 2001)

R115777 Phase I with 1-2 agents, activity observed in leukemia and breast cancer. MTD 400 mg bid + GEM 1000 mg/m2 + CDDP 75 mg/m2 (5/18 OR) (ASCO 2001). Combined to Herceptin in breast ca both at full doses. (ASCO 2001)

T Brunner et al (Ca Res 203;63:5656-68). Review R115777. 8 Phase II indicated modest activity in AML & MDS. Rest no OR observed. 2 Phase III trials: Pancreas (+GEM vs GEM alone) no differences (N=688); CRC (vs placebo) No differences (N=350). Combine with RT or other Chx?.

H MacKay et al (Clin Ca Res 2004;10:2636-44). BMS-214662, 200 mg/m2 + CDDP 75 mg/m2. Phase I . Inhibited FTI. Diarrhea, neuropathy, liver toxicity.

B Friday & A Adjei (Clin ca Res 2008;14:342-6). Ras mut present in 30% cancers, (pancreas 90%, CRC 50%), B-Raf mut melanoma 63%, papillary thyroid 45%, low grade ovary 36%. Small molecule inhibitors: PD098059 poor pharmacologic

properties; U0126 (also poor pharmacology), CI-1040 inactive clinically, AZD-6244 better than CI-1040 500-3000 mg bid, on going, PD-0325901 1-30 mg bid, blurred vision, rash, anemia, ERK suppression 84% and >2 mg bid and 2 PR in melanoma.

A. Adjei et al (JCO 2008;26:2139-46). AZD-6244 (inhibitor MEK1/2). Phase I. MTD 200 mg bid poorly tolerated had to be reduced to 50% and MTD 100 mg bid. Rash. Reduced ERK phosphorylation by 75%. N=57. 9 NC>5 mo (thyroid, RCC, melanoma).

M. Beeram et al (JCO 2005;23:6771-90). Raf is phosphorylated at serine/threonine residues. Raf is downstream of Ras and one common pathway MAPK-MEK-ERK pathways of cancer. Activating ras mutations (22% NSCLC, 50% CRC, 90% Pancreas, 25% cholangiocarcinoma, 23% H&N, 50% ovary. B-Raf mutation (V599E) occur in 60% melanoma, 83% anaplastic thyroid carcinoma, 40% papillary thyroid, and 2-5% miscellanea; C-Raf mut present in 90% SCLC. Therapy: ISIS 5132 antisense oligonucleotide (ASON) inactive. Sorafenib, 400 mg bid, active in B-Raf, EGFR2, PDGFRB, Flt3, c-kit, p38a, and inactive in EGFR, HER2, IGFR1, c-met, PKA & others. Results in RCC single agent perhaps through VEGFR were positive with MOS prolongation; melanoma in combination to CDDP+TXL showed 40% PR + 43% NC, and was unrelated to B-Raf mutaton status; pancreas cancer in combination with GEM had advantage in PFS.

Inhibidores de bcr-abl:

STI-571. Muy activo en LMC, y recientemente en sarcoma del estroma intestinal (NEJM, 5 abril 2001) MRD >300 mg/dia, oral. Comparte receptor con PDGFr, c-kit y por lo tanto puede ser activo en glioma multiforme, mielofibrosis, ca prostate y SCLC, entre otros. Glivec 300 mg/d (ASCO 2001)

K Bepjun et al (JNCI 2004;96:46-55). Imatinib inhibits growth of neuroblastoma cell lines in Vitro and in vivo, and suppress PDGFR, c-kit and VEGF expresión.

E. Berman et al (NEJM 2006;354:2006-13). High dose Imatinib correlate with high P urinary excretion, low serum phosphates (2mg/dl, N>2.5), low-normal serum calcium and elevated PTH.

DASATINIB (Sprycel, BMS) approved by FDA for Gleevec resistant CML, 70 mg qd po. MCyR 45%; Complete CyR 33%; Major Hematol Resp 59% acute phase, 32% Blast phase, 31% Lymphoblast phase, and 42% ALL-Ph+.

Multiple TKI (Inhibidores de tirosine kinases):

Imatinib	kit	PDGF				BCR/ABL
Sunitinib	kit	PDGF	VEGF1,2,3	FLT3	RET	
AMG706	kit	PDGF	VEGF1,2,3	FLT3	RET	
Sorafenib	kit	PDGF	VEGF1,2,3			RAF,BRAF ERK
Vatalanib	kit	PDGF	VEGF2	FLT3		FGF EGF
Pazopanib	kit	PDGF	VEGF1,2,3			

SU 101.Inhibe PDGF TK. MRD 440 mg/m2 civi 24 h Semanal x 4 q 6 sem. Respuesta glioma anaplasico. Vida media >20 dias. Toxicidad: Nauseas y vomitos.
CEP 751. Inhibe trk TKR. Alguna respuesta en ca próstata.

D Sharker et al (Clin Ca Res 2008; 14:2075-81). TKI 258 (CHIR-258), inhibitor of VEGFR 1,2,3, PDGFRB, FGFR 1,2,3, Flt3, Kit, Ret, TRKA, CSF1. Phase I MTD 125 mg/d. N&V, fatigue, headache, anorexia, diarrhea, hypertension. OR: 1 PR melanoma, 2 NC>6 mo GIST.

D Cenihan (JCO 2008;26:5154-5). Sunitinib: LVEF decrease>10% in 11-30%, Heart failure 3-5%, hypertension 30-45%, cardiac ischemia 10-15%. Sorafenib data 5% LVEF, 10% hypertension and 5% iscehmia. Need of cardiac monitoring and team approach.

C London et al (Clin Ca Res 2009;15:3856-65). Palladia (SU-11654). TKI for kit, PDGFB, VEGFR2. Dogs with mast cell tumor (kit mut) 3.25 mg/kg vs placebo qod x 6 wk, had ORR 37.2% vs 7.5% and at cross over OR 41.4%. MRD 12 mg wkly and MTTP 18.1 wk.

N Van Erb et al (JCO 2009;27:4406-12). Sunitinib toxicity pharmacogenomics: Leukopenia correlated with: CYP1A1 2455A/G, OR=6.24; Flt3 T238T/C OR=2.8; or abscense of CAG in NR1/3 OR=1.74. Mucositis correlated with: CYP1A1 2455A/G OR=4.03; and Hand-foot syndrome correlated with ABCB1 TTT haplotype (3435C/T, 1236C/T, 2677G/T) OR=2.56.

Inhibidores de EGFR-TK:

EGFR overexpression: NSCLC 50%, RCC 75%, Urothelial cancer 60%, Endometrial ca 60%, GBM >75%, CRC <25%, Melanoma >75%, MFH >50%, H&N 50%.
HER2 overexpression: Breast ca 29%, Mesothelioma >75%, GBM >75%, CRC 50%, Ovary 50%, Urothelial 50%, Gastric <25%, Prsotate inn high Gleason 50%, Páncreas 75%, H&N, Meningioma
c-kit: GIST 90%, almost all Endometrial,Thyroid, SCLC, Sarvcomas, ovary, melanoma, GBM and 50% in NSCLC, páncreas, but <20% breast and prostate.

J Baselga (JCO 2006;24:2225-6). EGFR overexpression due to amplification sensitive to drugs antiEGFR. In case of mutation Erlotinib and Gefitinib sesitivity correlate with substitution G719 exon 18, exon 19 in-frame deletions, exon 20 in-frame insertions, substitution L858/L861 in exon 21. For the contrary, T790M mut is resistant to Erlotinib and Gefitinib and also Exon 290 insertion resistant mutant is sensitive to EKB569, HKI272, CL-387, CL785 and CI-1033.

Iressa: ZD1839 Inhibidor de EGFR-TK. MRD 300-400 mg hasta 1 g/dx 28 dias, Toxicidad: Diarrea, cutánea. Respuestas en cabeza y cuello y NSCLC.

Tarceva: OSI-774, 150 mg qd. DLT diarrea, RASH. Ro: CABEZA Y CUELLO, OVARIO, nsclc

Cetuximab C225, 400 mg/m2 loading and then 250 mg/m2 wkly. Clinical studies in H&N, CRC, RCC. Combination with Chemnotherapy in CRC 25% OR with CPT and OS improvement.

AR Tan et al (M Hidalgo) (Clin Ca Res 2006;12:6517-22). Cetuximab PK indicates 250 mg/m2 is correct and can be given every 2 wks, otherwise accumulation occurs. Rash correlated with response.

P Fracasso et al (Clin Ca Res 2007;13:986-93). Cetuximab 250 mg/m2 saturates EGFR. PK lineakl up to 400 mg/m2. Recommend 250 mg/m2. Rash correlated with OR nad higher Cetuximab levels.

Panitumumab, ABX-EGF 2.5 mg/kg wkly x 4 & qowk. CRC OR 6% & NC 50%

Lapatinib (GW572016) reversible inhibition ErbB1, ErbB2 TK. Biopsy data showed OR in 4 breast cancer and 11 NC with different tumors. Response correlated with inhibition of TK and increased cell apoptosis

H Burris III et al (JCO 2005;23:5305-13). Lapatinib Phase I. MRD 500.1600 mg qd po. N=67. OR in patients overexpressing ErbB1 & ErbB2. 4 OR in Herceptin rersistant breast cancer.

C Erlichman et al (JCO 2006;24:2252-60). EKB569 Phase I: MTD 75 mg and

MRD 50 mg po qd. DLT: Diarrhea grade 3,rash, nausea, asthenia

CP 358774. MRD 150 mg/d. Respuestas NSCLC, H&N, CRC. Toxicidad: diarrea, rash cutáneo, fatiga.

SU5416 (anti Flk1-KDR is active in AIDS-Kaposi: 1CR, 4PR, 11 NC, 1 PD (ASCO 2000) SU6668 (TKI importente en angiogenesis) en estudio Fase I 300 mg/m2 bid con la comida (ASCO 2002, Abs 335)

GW572016 inhibidor doble de EGFR y erbB2 en Fase I hasta dosis de 175 mg/d con minima toxicidad (rash, digestiva y hepatica) (ASCO 2002, 374)

CCI-779, inhibidor de mTOR kinase NC en renal ca (ASCO 2002, Abs 36)

CI-1033, inhibidor pan.erbB, dosis escalada hasta 220 mg/d con toxicidad minima (ASCO 2002, Abs 41)

CI-1040. inhibidor de MEK1 y MEK2 kinasas, 800 mg/tid con la comida (ASCO 2002, 320).

A Reid et al (EJC 2007;43:481-9) Inhibitors EGFR+HER2: Lapatinib 1200-1500 mg qd OR 22-38% in Herceptin resistant breast cancer. Pertuzumab (Genentech, Omnitarg) 420 mg q 3 wk. OR 4.3% in ovarian cancer, no OR in prostate cancer and NC 42% in NSCLC. Herceptine+Cetuximab?.

I Duran et al (Clin Ca Res 2007;13:4849-57). Phase I Sorafenib first wk and then Sorafenib 400 mg bid + Erlotinib 150 mg qd. N=17. Fatigue, diarrea, rash. OR: 3 PR + 9 NC (Cholangioca, small bowel ca, glucagonoma).

E. Kwak, J Clark & B Chabner (Clin Ca Res 2007;13:5232-7). Combination of target agents: PI3K + Trastuzumab or TMX restore sensitivity (Rapamycin?) in breast cancer; PI3K + Ras inhibitor in GBM; Dasatinib + Imatinib in CML; Sunitinib + Imatinib in GIST; Lapatinib + Trastuzumab in breast cancer; 17AAG + Imatinib or Trastuzumab in CML/Breats cancer; antiapoptotic + Antiangiogenesis; Antiangiogenesis+ others.

LS Rosen et al (JCO2007;25:2369-76). AMG706 (TKI VEGFR 1,2&3, PDGFR, SCFR) Phase I: MTD 125 qd po. Diarrea, fatigue, N&V, Hipertensión. N=100. OR 7% + NC 49%. There were 3/7 OR in thyroid cancer.

KK Wong et al (Clin Ca Res 2009;15:2552-8). Neratinib (HKI272), Pan ErB TKI (ErbB1 and HER 2). Phase I MRD 320 mg/m2. Rash< Erlotinib, diarrhea. In 25 breast can >HER-2 resistant 7/8 PR, overall 35%, promising agent; and in 14 NSCLC 6 NC that all had EGFR mut, otherwise no effect.

Inhibidores de ILGF-R1:

BS Miller et al (ca Res 2005:22:10123-7). IGFRR1 is not samplified or mutated but regulates cell proliferation, survival and metastases. CP-751 MoAb to receptor IGF in trial in myeloma. Another approach is TKI inhibitor NVP-AEW541

D Yin et al (Clin ca Res 2007;13:1000-9). Pegvisomant sc qd x 14 d 40 mg induced a 5/% IGF-1 inhibition, 60 mgqd increased to 61%, 80 mgqd increased to 80% inhibition, lasting 21 d after a maximal suppression at d7. Compared to Octreotide this had only 33% IGF-1 inhibition. Adverse effects headache and fatigue. These results open a possibility to treat solid tumors with expression of IGF1 & 2 (CRC, breast, prostate) in addition to neuroendocrine tumors.

E Rowinsky et al (Clin Ca Res 2007;13:5549s-55s). IMC-A12 (MoAb to ILGF-R1 active in vitro and in solid tumors and xenografts which enhance cytottoxic drugs (alkylating agents, Pt derivatives, Vincas, TXns, others). Interaction with PI3K/Akt/mTOR and also RAF/MEK/ERK pathways. Early clinical trials with doses 3-10 mg/kg indicated 2 NC breast and HCC.

Inhibidores de SRC:

L Song et al (Ca Res 2006;66:5542-8),. Dasatinib tried in lung cancer cell lines and EGFR mut induced apoptosis due to down reguklation Akt and STAT-3, as compared tyo EGFR wt where indiuced G1 cell cycle arrest (prevent invasion).

JM Summey ey al (Clin Ca Res 2006;12:1398-401). No receptors for Src-TK, but intermediates signaling in multiple patways (PI3K, STAT-3, P38MAPK, Ras, INK, Paxillin and p160CAS, which may be of therapeutic interest.

Inhibidores de HGF/MET:

L Toshi et al (Clin Ca Res 2008;14:5941-6). Papillary RCC, GI cancer, GBM, NSCLC. AMG-102 Mo Ab anti HGF/MET, and other TKIs: XL880, XL184, SGX523, PF02341066, JNJ38877605, ARQ197, MGCD265.

9.- Epigenetic therapy: Histone acetylation and hypomethylation

DNA Methyltransferase-1 (DNMT-1) inhibitors: 5 Azacytidine (Vidaza) FDA approved MDS; 5Aza-deoxycytidine (Decitabine) FDA apporved MDS (Low dose results/effects?); Arabinosyl-5Azacytidine (Fazarabine); Epigallocatechin-3.gallate; MG98 DNMT-1-antisense; Zebularine

Histone deacetylase inhibitors (HDAC): Butyrates FDA approved in urea cycle disorders; SAHA (Vorinostat, ZOLINZA) FDA approved CTCL (OR 30%, Toxicity: DVT, PTE, Thrombocytopenia, anemia, GI, hyperglycemia, QT prolongation, do not combine with valproidc acid; Valproic acid (Depakine) FDA approved antiseizure; Depsipeptide; MGCD0103

DNMT-1 inhibitor followed by HDAC inhibitor: expect a synergistic effect

L Kopelovich et al (JNCI 2003;95:1747-57). The epigenome is a possible target for cancer chemoprevention because hypermethylation occurs very frequently in common cancers. Agents include: DNA methyltransferase inhibitors (5 Azacytidine, 5 Aza-2-deoxycytidine, Zebularine, MG98 antisense oligonucleotide) and Histone deacetylase inhibitors (Depsipeptide, MS275, Oxamflatin, Pyroxamide, Butyrates, Suberoylanilide Hydroxamic acid (SAHA), Trichostatin A, Valproic acid) and both mechanisms are synergistic.

WK Kelly et al (Clin Ca Res 2005;9:3578-88). Phase I SAHA (Suberoylanilide Hydroxamic acid) iv 75-900 mg/m2. Toxicity hematological. MTD 300 mg/m2/d x 5 wkly x 3 q 4 wk in hematological tumors. Accumulation of histones (acetylated) was observed in PBLs. OR: 2 NHL and 2 bladder out of 29 patients.

B Segura Pacheco et al (Clin Ca Res 2003;9:1596-603). Hydralazine and procainamide (cardiovascular antiarrythmic drugs) are hypomethylating agents with a potential activity in adjuvant therapies.

******PA Jones and R Martenssen (Ca Res 2005;65:11241-5). AACR sponsored launch of a multi-tiered epigenome project using the following techniques: ChIP (Chromatin immuneprecipitation microarray requiring 20 g of chromatin; DNA methylation analysis of all human genes in major tissues; SAGE-linked methylation and chromatin analysis; Histone modification in imprinting; Small RNA role in epigenetic control; Application to selected tumors (CRC, breast, NB, CNS).**

O´Connor et al (JCO 2006;24:166-73). SAHA Phase I po/iv. N=39. Results: 1 CR SLL, 1 PR DLCD, 1 PR HD, and 3 SD (HD, DLBCL, CTCL) appering active at tolerable doses. OR po 20% and iv 20%. Other agents include: Phenylbutyrate with observed hematological tumor activity, Depsipeptide active in CTCL 8/14 OR. SAHA in CTCL 5/13 OR (38% continuous schedule and 17% in intermittent schedule).

EH Rubin (Clin Ca Res 2006;12:7039-45). Vorinostat 400 mg single dose fasting d 1 & 5 or 400 mg qd x 7 or 28 d. PK similar after single or multiple doses. Recommend 400 mg qd.

F Giles et al (Clin Ca Res 2006;12:4628-35) LBH589 Hydroxamic acid analogue

HDAC inhibitor. N=15 AML, ALL, MDS. Phase I: <11.5 mg/m2, consistent biological effect: low K ion 27%, N&V 40%, diarrhea 33%, and antileukemic effect 8/11.

S Ramalingam et al (Clin ca Res 2007;13:3605-10). Vorinostat 400 mgpo qd x 14d or 300 mg bid x 7 d + CBDCA AUC 6 + TXL 200 mg/m2. OR 11/25 + NC 7/25 (NSCLC, H&N untreated).

P Münster et al (JCO 2008;25:1979-85). Valproic acid MTD 140 mg/kg/d 1-3 (48 h) po for a total dose of 8-10 g + EPI MTD 100 mg/m2 d3, repeated q 3 wk. OR 22% (9/48) + NC 39%. Prior anthracycline 25%. Benefit: 5/11 melanoma, 7/10 breast, ¾ SCLC, ½ prostate, suggesting imporvement over EPI effects.

NL Steele et al (Clin Ca Res 2008;14:804-10). Belinostat (HDAC inhibitor) MTD 1000 mg/m2/d x 5 d in 30 min iv q 3 wk. DLT fatigue, diarrhea, N&V. Histone H4 deacetylation obeserved lasting 4-24 h and elevation IL6. NC 18 (39%) at MTD NC 50%.

F Braiteh et al (Clin Ca Res 2008;14:6296-301). Combination 5AZA sc qd x 10 MTD 75 mg/m2 + Valproic acid po 10 mg/kg/d up to 60 mg/kg /d to reach alevel 75-100 ug/ml (above excessive somnolence). N=55. 14 NC (25%), fever, ANC, platelets. Not superior to 5AZA alone!.

R Plummer et al (Clin Ca Res 2009;15:3177-83). MG98 (oligonucleotide antisense), CIVI x 7 d q wk 100.250 mg/m2/d; MTD 200 mg/m2/d. Consistent suppression of DNMT1 expression in 26/32 patients. 1 OR esophageal + 1 NC GIST prolonged >3y.

P Munster et al (Clin Ca Res 2009;15:2488-96). Valproic acid po loading 120 mg/kg followed by 60 mg/kg q 12 h x 5 d followed by FEC in breast cancer. OR 64% breast cancer without prior exposure to Doxo; other OR in prostate, pancreas, cervix, melanoma, etc.

J Lin et al (Clin Ca Res 2009;15:6241-9). 5Azacytidine 10-25 mg/m2 d 1-14 (or 75 mg/m2 d 1-7, or 10-12.5 mg/m2 d 1-21) + Sodium phenylbutyrate (400 mg/m2 d 6 & 13, or d 8-14, or d 6, 13 & 20). No effect in solid tumors. Minor myelosuppression, neutropenia and anemia. Disappointing: 1NC + 26 PD…

10.- Inhibidores de proteinas

Ansamycin benzoquinones: **17AAG** (Geldanamycin) Union a **HSP 90** causando depleción de proteinas oncogenicas. Hsp-90 targets all the six hallmarks of a cancer cell (Hanahan and Weinberg (Cell 2000;100:57-70): self sufficiency in growth signals; evading apoptosis; insensivity to antigrowth signals; sustained angiogenesis; limitless replicative potential; and tissue invasión and metastasis.

R Ramanathan et al (Clin Ca Res 2005;11:385-91). Phase I 17AAG: 295 mg/m2 wkly x 3 q 4 wk. PK lineal. Toxicity 30% reversible liver enzymes.
M Goetz et al (JCO 2005;23:1078-87). Phase I 17AAG 308 mg/m2 d 1, 8 & 15 q 4 wk.
R Ramanathan et al (Clin Ca Res 2007;13:1769-74). 17AAG biwk, MRD 175-200 mg/m2. DLT: liver, N&V, headache. PBL HSP-70 increased from x0.8 to x30

B Cullinan et al (Sem Oncol 2006;33:457-65). HSP-90 inhibition leads to multiple inhibition pathways but so far no activity has been found using 17AAG (Geldanamycin) in combination chemotherapy (NC in melanoma only). Drivatives are being developed because formulation is difficult.

B Gyurkocza et al (JNCI 2006;98:1068-77). Shepherdin inhibit Hsp-90 and activity has been identified in AML (not AMML) inducing cell death in vitro…

SH Oh et al (JNCI 2007;99:949-61). Deguelin is a rotenoid which binds to Hsp-90, suppresses its function and degrade HIF-1a. It is active in tumor xenografts.

Inhibidor de proteasome: **PS 341.** Degrada proteina ligadas a ubiquitina. Respuesta en próstata y pulmon. MTD: 1,8 mg/m2. PS341 1,3 g/m2 iv d 1 &4, 8 &11, q 3 sem x 8 activo en Mieloma multiple: 18%RC, 28% RP en paraproteina (ASCO 2002, Abs 40)

H Ludwig et al (Cancer 2005;104:1794-807). Bortezomib activity: Myeloma Phase II CTR 10-30%+ PR 16-30%, and Phase III Bortezomib>Dexamethasone in OR/OS, and Front line therapy OR>90%; AML: combined to IDA+AraC; MCL OR 40%; NHL OR 30%; Waldenstrom OR 20%; HD OR 20%; Solid tumors: No effect in breast, prostate, RCC 10% and NSCLC 4-10%. Toxicity neuropathy 10-15%, thrombocytopenia 25%, fatigue 12%, rash 1%, GI 25% and rarely tumor lysis.

G Ayala et al (Clin Ca Res 2008;14:7511-8). Bortezomib given preoperatively in prostate cáncer: enhanced NFkB, increase Src-3and Akt, can be combined to Perifosine to enhance Akt inhibition, and showed in most of the patinets a decrease in PSA.

R Orlowski et al (Clin Ca Res 2008;14:1649-57). Bortezomib new generation:

Carfilzomib (PR-1171) and Salinosporamide (NPI-0052) are active in Bortezomib resistant tumors due to irreversible binding to 26S proteasome. Activity identified in MM, CLL, Waldenstrom.

Dietary methionine restriction (0.8 g methionine free protein/kg/d) cause s weight loss of 0.5 kg/day and mild reversible fatigue, giving 3/9 OR (prostate and others). Confirmed plasma methionine reduced from 22 uM to 9 uM while albumin remained stable (AACR 2001) (2908)

AHM Reid et al (Clin Ca Res 2009;15:4978-84). CHR-2797 (Tosedostat) inhibitor of M1 Aminopeptidase more potent than Bestatin. N=40 solid tumors. MRD po single agent 240 mg/d. Txicity: Thrombopenia, dizziness, anemia, fatigue, diarrea, edema. Results: 1 PR in RCC+ 4 NC>4mo.

11.- Agentes moduladores de la resistencia a farmacos

Tirapazamine. Agente toxico selectivo para celulas hipoxicas. Es un sustrato de la reductasa, que reacciona con hidrogeno de DNA produciendo roturas de la hebra. En condiciones aerobicas el oxigeno quita el electron adicional de la Tirapazamoine dejando el farmaco inocuo y un radical superoxido (menos toxico que Tirazapamine-radical). Estudios clinicos han demostrado potenciacion de la RT en cancer de cabeza y cuello y beneficio en asociacion con CDDP en NSCLC (ambos en estudios controlados). Investigacion activa en combinacion con quimioterapia.

TER 286: Activacion en celulas tumorales resistentes a quimioterapia que expresan glutathione S-transferase.

Incel, VX70 , bricodar dicitrate inhibe Pgp y MRP-1. Respuestas en ovario, sarcoma, mama próstata.. MRD 120 mg/h steady state

PSC 833. Valspodar. Inhibe mdr. MRD 5 mg/kg/qdx 12 q 3 sem, via oral.

A Sandler et al (Clin Ca Res 2004;10:3265-72). Zosuquidar trihydrochloride (LY-335979) associated to DOXO 45-75 mg/m2, Phase I. MTD 640 mg/m2 (48h iv) prior to DOXO. PK demonstrated at doses >500 mg/m2 increase in AUC of DOX 15-25%, more cytopenia nad NK PgP inhibition.

J Abraham et al (Clin Ca Res 2009;15:3574-82). Tariquidar (XR-9576) anthranilic acid derivative and selective PgP inhibitor. Phase I 150 mg in 30 min iv infusion associated to NVB 20 mg/m2 d 1 & 8. Side effects: pain, anorexia, fatigue, myalgia, diarrhea, depression. Inhibit liver PgP (reduced Tc99m sestamibi), increased tumor retention of drugs, blocked PgP rhodamine efflux from CD56+cells, no effect on NVB kinetics.

********R Oostendorp et al (Clin Ca Res 2009;15:428-33). Ritonavir (antiCYP3A4 and antiPgP used in HIV) 100 mg po d 1 & 2 + Docetaxel 100 mg or po: Oral bioavailability of TXT increased 131-161%, remarkable improvement!.**

12.-Farmacos moduladores de la apoptosis

Apoptosis inhibition:First site of apoptotic disturbance are the death receptors;

second site mitochondria; Third site caspases.
Pro-Apoptotic Chemoprevention of cancer is of great interest because takes shorter time than differentiating therapy and is a very potent highly conserved mechanism useful to destroy unwanted cells, non toxic to tissues. Mechanisms are extrinsic via TNFR, Fas, TRAIL, and inducing caspase 8, activation of caspase 8 that result in a proteolytic cascade; and intrinsic via Bcl2 in the outer side of mitochondria which activate proapoptotic signals (Apaf-1, caspase 9) family members of inner side of mitochondria which trigger caspase 3. Agenst include: retinoids (all trans, Retinamide), NSAIDS (ASA, sulindac, celecoxib, indomethacin), Polyphenols (Resveratrol, Epigallocatechin gallate), Butyroid (Tributyrin), TMX, Genistein (Flavonoids), Vanilloids (Capsaicin, Curcumin, Resinferatoxin), Rotenoids (Rotenone, Deguelin), etc.

M Schön et al (JNCI 2003;95:1138-49). Imiquimod (imidazoquinoline derivative) induce apoptosis through caspase 3 activation not related to membrane death receptors (Fas, TNF, Trail). Topical application in skin cancer circunvents mechanisms developed by tumor cells to resist apoptotic signal.

LS Rosen et al (Clin Ca Res 2003;9:1628-38). TLK-286 (Glutathione S Transferase P1-1, activated glutathione analogue) induce apoptosis via stress response pathway MAPK, MEK, JNK→caspase 3. Phase I MRD 960 mg/m2 iv 30 min q 3 wk. Results: mR 3/35.

A Tolcher et al (JCO 2007;25:1390-5). Mapatumumab (MoAb against TRAIL-R1) 10 mg/kg q 14 d. Fatigue, fever, myalgia. Results: 19/49 NC for 9 mo. Importantly 68% of tumors express TRAIL-R1.

R. Plummer et al (Clin Ca Res 2007;13:6187-94). Lexatumumab (activate TNF-TRAIL-R2). Phase I: 30-120 min iv q 3 wk 0.1-20 mg/kg. DLT 20 mg/kg, transaminitis, increase in amylase and bilirubin. Terminal half life 6-16 d. N=37, 12 NC >4.5 mo (3 had STS). MRD 10 mg/kg q 3 wk.

S Bonnet et al (Cancer Cell 2007;11:37-51). Dichloroacetate blocks mitochondria activity and promote apoptosis. Active in rat model…

B Pardo et al (Clin Ca Res 2008;14:1116-23). Kahalalide Phase I as 1 h wkly. MTD 800 ug/m2 → MRD 650 ug/m2. No accumulative toxicity, no hematological, DLT liver enzymes. OR observed in melanoma, NSCLC & NC in breast, pancreas.

SR 45023 A: Interactivo con receptor FXR (death receptor)

Agentes mitocondriotoxicos:
Acido betulinico, PK11195 y RO54864 (ligando de receptores de benzodiacepinas), Lonidamine (Indazole carboxylic acid), MKT 077 (colorante de Rhodacyanine), y Peptidos (KLAKKLAK)2

Analogos de ceramide son inductores de apoptosis, medido por el nivel de caspase-3. En modelo raton no es toxico y mejora supervivencia. El compuesto seleccionado se denomina AL-6 (S Fogli et al, PISA, Ann Oncol 2000;11: Suppl2)

Trisenox (AS_2O_3)

Aprobado por FDA para la leucemia promielocitica aguda (70% RC), 0,15 mg/kg/d iv en 11-2 h por <60 dias y consolidacion despues con misma dosis por 25 dias (en 5 semanas) Efectos secundarios: Fatiga, fiebre, edema, nausea y vomitos, anorexia, diarrea, dolor de cabeza, insomnio, tos, disnea, dermatitis, taquicardia, dolor, hipokalemia, hipomagnesemia, hiperglucemia. Toxicidad grave: Neutropenia, trombopenia, hipokalemia, sepsis y arritmia cardiaca

D Douer et al (JCO 2005; 23:2396-410). As_2O_3 active in APL. Activity found in Myeloma 21% (inductor of apoptosis through NFkB and glutathione supression).

AM Tsimberidou et al (Clin Ca Res 2009;15:4769-76). Darinaparsin (organic arsenic). N=40 solid tumors. Phase I, MRD 300 mg/m2 qd x 5 q 4 wk. Toxicity mental, ataxia. Results: 17.5% NC>4 mo (4 CRC, 2 RCC).

ANTI bcl-2

1.-Non peptide inhibitors: Gossypol, ABT-737

2.-Oligonucleotides antisense:

Genasense (antisense to 6 first codon of bcl-2 mRNA downregulates bcl-2) 5-7 MG/KG/D civi x 5 d + TXT, 60-100 mg/m2 in HR prostate cancer (OR 4/8), downregulates bcl-2 in vivo (ASCO 2001)

F Cotter et al (Sem Oncol 2004;31:18-21). Oblimersen (Genasense, G-3139) Phase I up to 147 mg/m2/d total. DLT 4.1 mg/kg/d cytopenia, renal, hypotension. MRD: 1-3 mg/kg/d civi 5-7 d (inhibit bcl2. Activity: NHL N=21, 1 CR>3y + 2 mR + 9 NC; Melanoma (+DTIC) N=14: 1 CR + 2 PR + 3 mR.

MJ Millaward et al (Proc ASCO 2004;708:7505). Melanoma Randomized N=771, MFup >12 mo. Randomized Oblimersen + DTIC (PFS 74 d, OR 13%) vs DTIC (PFS 49 d, OR 7%, non significant differences). Other studies pending rersults: Phase III NSCLC Oblimersen + TXT vs TXT, Myeloma Oblimersen + DXMTS vs DXMTS; CLL Oblimersen + Fludara + CPA vs CPA+ Fludara). Other Phase II: Esophagus, CRC, Breast, Prostate.

S Rheingold et al (JCO 2007;25:1512-8). G-3139 Oblimersen 7 mg/kg civi x 7 d + DOX 30 mg/m2/d 5 & 6 + CPA 500 mg/m2 d 5 & 6 + GCSF. Results: 11/15 reduction bcl2 in PBMN

MH Kang et al (Clin Ca Res 2009;15:1126-32). Review Oblimersen: Myeloma no significant activity with Oblimersen+ DXMTS; Melanoma FDA dismissed DTIC+/- Oblimersen; CLL FDA pending Oblimersen +/- FLU-CPA (OR 7% vs 17% but OS 40 mo , p<0.05); NSCLC Oblimersen*/-TXT nas SCLC Oblimersen +/-PE on going no OS benefit; AML Oblimersen+DAUNo-ARAC no activity. Studies

pending results: Myeloma DXMTS+THAL+/-Oblimersen; HCC DOX + Oblimersen; RCC IFNa + Oblimersen. Review small molecule BCL2 inhibitors: Gossypol AT-101, Apogossypol, BH31S, ABT-737, ABT 263, GX-15-070

SURVIVIN INHIBITORS

AW Tolcher et al (JCO 2008;26:5198-203). YM-155 (small molecule inhibitor of survivin which binds to SMAC and prevent inhibition of caspase activation and apoptosis, leading to cell death due to control of antiapoptotic signals). N=41. Dose range 1.8-6 mg/m2/d (civi 7 d) q 3 wk. MTD 4.8 mg/m2. Toxicity: creatinine, acute tubular necrosis. Results: NHL 1 CR + 2 PR, HRPC 2 PSA responses, NSCLC 1 mR. Very good preliminary results.

T Satoh et al (Clin Ca Res 2009;15:3872-80). YM-155 survivin suppressant, Phase I, MTD 8 mg/m2/d in 7 d civi. Toxicity: creatinine, microalbumin in urine, fever, fatigue, anemioa. Results: 9/33 NC (MFH, thymoma, NSCLC).MTD

CHEMOPREVENTION

Bexarotene (gel de Targretina al 1%, tratamiento topico) Aprobado por FDA para linfoma cutaneo T en estadio IA/IB (26% RC)

S Lam et al (JNCI 2002;94:1001-9). ADT (anethole dithiolethione, approved for insalivation after RT in Europe), 25 mg tid used in chemoprevention of lung cancer with patients with biopsy proven dysplasia and severe smoking history. Randomized ADT (N=61, worse 8%, Progression rate/person 32%) vs placebo (N=51, worse 17%, Porgression rate 59%). Mild GI symptoms. Active!...

B Psaty et al (NEJM 2005;352:1133-4). Editorial. COX-2 inhibitors associate with an increased risk of cardiovascular complications (AMI. Stroke, heart failure and hypertension) RR=2,8 for rofecoxib, and celecoxib. No final definitive results are available (analysis of risk vs benefit) and prior history and risk factor assessment is recommended.

J Mao et al (Clin Ca Res 2003;9:5835-41). Celecoxib inhibits PGE2 alveolar production in smokers. PGE2 confer the malignant phenotype to the cells…Uinterest in chemoprevention.

A Duffield-Lillico et al (JNCI 2004;23:1729-31). B-carotene trial in lung cancer demonstrated an increase in the incidence of lung cancer (17%) due to conversion to pro-oxidative drug (high dose). Problem was to enter a large trial without prior Phase I-II data.

D Alberts et al (Clin Ca Res 2004;10:1875-80). High dose Vit A vs Placebo 25000-75000 qd x 12 mo protected skin cancer in patients with severe actinic keratoses. MRD 25.000 iu/d.

M Graaf et al (JCO 2004;22:2388-94). Statin use decreased cancer incidence 20%, overall data and all tumor types…

Y M Adhami et al (Clin Ca Res 2006;12:5611-4). Natural products interferring with IGFI & II could be used in chemoprevention. IGF-1 pathway stimulate TK proliferation mediated Raf, MEK, ERK, and phosphorylation IRS1, PI3K, Akt, mTOR. Inhibitors are: tea polyphenols, lycopene, curcumin, sibilinin, apigenin. IGF2 is inhibited by resveratrol.

S Bonovas et al (JCO 2006;24:4808-17). Review metanalysis of all chemoprevention trials (N=109.143). NO protective anticancer effect RR=0.99. Age of participants modified the results and median follow up was very short (median 4.5y). Non confirmatory results.

B Jung (Ca Res 2006;66:9789-93). Melatonin (antioxidant) derived from Tryptophan has antiproliferative actions due to several mechanisms. Preliminary data and effect observed in RCC and melanoma, due to immune enhancement. Interest in chemoprevention.

R Govindarajan et al (JCO 2007;25:1476-81). Thiazolidinediones (oral

antidiabetes) are PPARg ligands (mediate cell cycle arrest in liposarcoma, NSCLC, CRC, adenomatous polyps and prostate cancer). TZD decreased lung cancer risk RR=0.67 in diabetic patients.