

CANCER DE VEJIGA URINARIA

DIAGNOSTICO PRECOZ

MICROSATELLITE URINE ANALYSIS

UPA & PAI related to tumor invasion

TGFBRI & II

TRAP (Telomeric repeat amplification protocol)

VEGF mRNA

Bcl2

c-met

CK 18 & CK20

Microarrays expression profiling (Ca Res 2004;64:4040-8).

B WG van Rhijn et al (Europ J Urol 2005;47:736-48): Most promising are
CYFRA21-1, Ck 20, Microsatellite analysis, BTA, ImmunoCyt, NMP22, UroVysion..

CANCER DE VEJIGA URINARIA- BIOLOGÍA MOLECULAR Y CARCINOGENESIS

Ta ->(9q22)-> T1 -> (9p21, 3p, 5q, p53)->T2-T4-> (11p, 6q, 13q, 18q) -> N+M+

9p21 (p15 & p16) cada un alterado en 18% (total 32%)

Hiperexpresion de erbB2 (17q21) 7%.

P53 alterado en 30%.

TGFBRI del 30%

Bcl2 alterado 40%.

HPV 16, 18, 33 presente en 30%.

P-gp presente después de quimioterapia en 30%.

Carcinógenos:

Arlaminas (aminas aromaticas de tabaco, colorantes, industria de caucho), edulcorante artificiales, esquistosomiasis, Arsénico, Analgesicos

Fenacetina HR=6.5; ciclofosfamida crónica HR=6.8

Aristolochia fangchi (hierba china para adelgazamiento) >200 g se asocia a cancer de vejiga urinaria.

Protectores:

N-acetil-transferase, CYP1A2N fenotipo oxidante, glutation-S-transferase.

Ingesta >2531 ml/d (HR=0.51).

Papilar de bajo grado es benigno y solo <5% metastatizan aunque 40% recidivan. Los carcinomas invasivos surgen de Ca in situ en vecindad. La citología + se debe a Ca in situ porque los pailomas benignos no exfolian. Cis no tiene grado celular, es siempre agresivo por definición alto grado; >30% desarrollan ca invasor en 5 años. Un error comun es confndir la muscularis de la lamino propia con la muscularis propia (>90% de las laminas propias tienen muscularis).

Papiloma urotelial invertido (casi siempre afecta trígono). Benigno, curación con resección local. Recidiva 1%

E. Messing et al (Cancer 2006; 107:2173-9). Chemical strip carried out at home to detect Hb in urine. Repeated at 6 months. Detect early high grade non invasive tumors without cancer mortality. N=1575; 258 positive; 212 bladder cancer distributed in stage and grade as observed in tumor registries but with less high grade and invasive tumors (only 10% as compared to 60% in unscreened tumor registries). Mortality at 14 y was 20% for registries and 0% for screened group. Ready for a early diagnosis trial?.

CARCINOMA UROTELIAL SUPERFICIAL

Tratamiento standard RTU y biopsia.

End point analysis should be time to invasion rather than time to recurrence.

Photofrin II (hematoporphyrin) 2 mg/kg iv followed by UV argon ion laser (RC 47%).

Tratamiento local: Tiotepa 30-60 mg intravesical q 4 sem (recidiva 50%)

Mitomicina C: 20-60 mg semanal x 8 (respuesta 75%, recidiva 50%)

Adriamicina 70-80 mg q 4 sem (RC 70% en Cis).

BCG>ADM (recidivas 58% vs 80%; MDR en Cis 38 meses vs 6 meses).

BCG> Mitomicina C

BCG> Tiotepa

BCG>VP16

MitoC > IFN alfa (Recidiva HR 0.82)

BCG: OR 60% en cancer residual, OR 75% Cis, MDR 70% a 5 años. Mecanismo: secreción de citoquinas IL1, IL2, IL6, IL8, IL10, IL12, IL18, GM-CSF, IFN γ , TNF, activación de CTL, T4, NK, macrófagos y neutrófilos, además actúa a través de MHC clases I & II, ICAM-1, FAS, CD40.

J Pow Sang & J Seigne (Cancer Control 2000; 7:335-9). Revision de cancer superficial. Factores de alto riesgo: recidiva múltiple, T > 3cm en diámetro, >3 lesiones; RTU incompleta; estadio T1 y T-Cis; y grado 3. El tratamiento intravesical con MitoC (0.5-2 mg/mL) 20-60 mg semanal x 6-8 semanas y mantenimiento posterior, comienzo de forma inmediata después de RTU, proporciona OR 45-60%, coste \$312; BCG 80 mg semanal x 6, mejor tasa de respuesta que MitoC, cistitis en >90%, coste \$157; IFN alfa 10-100 M UI semanal x 6, CR 66% después de recidiva a BCG, 17% toxicidad, combinación con BCG sinérgica, coste \$1210; Valrubicin: No toxicidad, RC 20% después de recidiva a BCG.

J Au et al (JNCI 2001; 93:597-604). N= 201 patients. Intravesical MitoC randomized to standard administration (20 mg in 20 mL water after Foley catheter drainage of bladder urine, retained 2 h, wklly x 6) TTR 11.8 mo; Relapse free survival 24.6% vs optimized (refrain from liquid intake for 6 h before until 2 h after the procedure, add Sodium

bicarbonate orally 1.3 g 18 h before, 6 h prior and 30 min before and remove residual urinary residuum at the time of intravesical treatment) TTR 28.1 mo and RFS 41%.

G Dalbagni et al (JCO 2002; 20:3193-8). GEM intravesical Phase I. MTD 2000 mg (range 500-2000) at pH 5.5 to avoid toxicity, biwk x 3 q 4 x 2 and then biopsy. N=18, refractory to BCG: 11 CR, minimal bladder irritation.

R Colombo et al (San Raféale, Milan) (JCO 2003; 21:4270-6). N=83. Randomization of N=83 to Hyperthermia (Medical Enterprises, Amsterdam; Synergo 101-1) + Mitomycin C 40 mg/50 mL (Recurrences 17%) vs Mitomycin C alone (recurrences 57%). Similar side effects.

A Giannopoulos et al (Clin Ca Res 2003; 9:5550-8). N=123, with T1 Ta grade <3, with a M F up 26.5 mo, randomized study comparing IFN alfa 1.5x10⁷ IU wkly x 8, q 2 wk x 4 & q mo x 8 (Tumor free 73.4%; cystitis at 6 mo showing T cell/macrophage, leukocyte and NK infiltration) vs MitoC 40 mg/50 mL and similar maintenance schedule (Tumor free 57.2%).

G Dalbagni et al (JCO 2006; 24:2729-34). N=30, M F up 19 mo. GEM intravesical in BCG refractory superficial bladder cancer refusing cystectomy. GEM 2000 mg/100 mL tiwk x3, one wk rest and repeat once more. OR 15 (50%); MRFS 3.6 mo; 1yRFS 21%. Cystectomy after GEM 37%.

**C Weiss et al (JCO 2006; 24:2318-24) Review high risk superficial bladder cancer defined as multiple in situ, grade III tumors, multiple focal lesions, tumor diameter >5cm and smaller tumors not qualifying if refractory to multiple TURs. In these cases TUR associated with a 80% recurrence and invasive tumors make up to 50-65% of them. BCG associated with a 30% recurrence rate. Cystectomy associate with a 70-90% cure rate with 20% morbidity and 1-4% mortality. Propose EBRT + ChX in T1 tumors fulfilling the mentioned criteria: EBRT 45-61.4 Gy and concurrent CDDP 25 mg/m²/d (or CBDCA) x 5 + 5FU 600 mg/m²/d x 5d, on d 1 and d 36 of EBRT. Results: CR 88% (121/137), 5y tumor progression 19% and 10 y tumor progression 30%; 5yDFS 82%; 5yDFS 73% (In CR 89% and 79% respectively); bladder preservation 80%; good urinary function 70.4%. Compared to BCG therapy is an improvement in 10% progression rate (25% to 15%) and in 20% in recurrence rate (50% to 30%).

**D Parekh et al MSKCC (JCO 2006; 24:5519-27). Review series of superficial bladder cancer: Ta 60%, T1 30%, Tis 10%, after initial TUR a second TUR indicated a 40% persistant disease. Recurrence rate >70% up to 10 y and 30% of recurrences had progression to higher grade /stage. ChX was MitoC initially; then BCG indicating a reduction of recurrence rate up to 50% in 5y and showing toxicity at high doses. Metanalysis of BCG reduction of 27% in progression rate but failure rate still >30%. Finally BCG + IFN alfa which indicated a reduction in recurrence rate >80%. Performed radical cystectomy when high grade recurrence or Cis refractory disease.

BA Inman et al (Cancer 2007;109:1499-505). PDL1 (Programmed cell death ligand 1, B7-H1) expresión correlated with poor prognosis in many tumor origins. PDL1 expression found very high in 11/12 patients with superficial bladder cancer who failed BCG.

K Esuvaranathan et al (Cancer 2007; 109:1097-105). Rb underexpression predicted more recurrences in superficial bladder cancer treated with BCG 30-80 mg (low dose) + IFN alfa (10 m U) x 2 cycles in 6 mo.

J McKiernan et al (JCO 2006; 24:3075-80). Phase I TXT 5 mg wkly x 6 in recurrent superficial bladder cancer. MTD not reached up to 75 mg/100 mL wkly. 56% NED; 44% grade 1-2 toxicity. Phase II planned.

CARCINOMA UROTELIAL INVASIVO

Supervivencia a 5 años con cirugía: T1 >80%, T2 70%, T3a 30-40%, T3B 15-25%. Global 40%-50%. Cis no significativo. Factores: >T2, invasión ganglionar, indiferenciación, márgenes positivos.

Importante distinguir T1 de tumores más profundos ya que la muscularis mucosa está ausente en 40% de las muestras y existe grasa en la muscularis en 30% de las muestras. Es por lo tanto recomendable medir la invasión en mm de profundidad desde la membrana basal o en caso de múltiples fragmentos estimar el menor diámetro de la muestra por RTU. T2 95% de diámetros >1.5 mm; >T3 en 83% mayores de 4 mm. Si se elige el cut off de 1.5 mm sensibilidad 81%, especificidad 83%, predicción positiva 95%, predicción negativa 56%: certeza global 0.89.

MSKCC repite RTU en todos los tumores resecaados endoscópicamente porque 40% demuestran tumor residual.

A Fleischmann et al (JCO 2005; 23:2358-65). N=507. Cystectomy + Careful lymph node dissection in three areas (external iliac artery, obturator fossa and internal iliac artery). MRFS 17 mo; MOS 21 mo. Univariate factors análisis: Stage T1-T2 vs T3-T4; lymph nodes positives <5 vs >5; rate of affected lymph nodes <20% vs >20%. Multivariate analysis only extracapsular invasion of lymph nodes (5 yOS 60% vs 18%). Some patients are cured by complete lymph node dissection.

D Parekh et al MSKCC (JCO 2006; 24:5519-27). Recurrence free survival in muscle invasive bladder cancer: T2 70-80%; T3 45-55%; T4 30-40% (N0 70% and N+ 30%). Lymphadenectomy important prognostic factor, radical cystectomy is preferred for quality of life (continence fails 30% of reconstructive techniques), neoadjuvant therapy is favorable in 3/11 trials with HR=0.85 (probably a power problem due to small series, and adjuvant not so clear results. This review had no consideration for EBRT techniques.

S Gilbert et al (Cancer 2007; 109:1756-62). Review of Quality of Life indexes indicated that intravesical therapy, TUR alone, and cystectomy + ileal conduit show minimal urinary leak (<25% daytime events and <10% nighttime events, while cystectomy + neo bladder showed daytime leakage 60% and nighttime leakage 80%.

Estudios randomizados:

Rafhavan-Wallace (Australia) N=255. EBRT+CDP vs EBRT. Resultados: No significativo.

Gospodarowicz (Canada) N=102. EBRT + CDP vs EBRT. Resultados: NS

Fossa (Escandinavia) N=300. CDP+ADM + Cistectomia vs Cistect.. Tendencia favorable

Mtnez Piñeiro (España) N=121. CDDP+ Cistectomia vs Cistect. NS

Crawford (SWOG) N=300. MVAC + Cistect vs Cistect. 5yOS benefit 15%. (37% pT0)

Hall (EORTC-MRC) N=1000. CMV+ Cistect vs Cistect vs CMV+ EBRT vs EBRT. NS (5% improvement in 3yOS)

Italia GISTV N=171 MVEC + Cistect vs Cistect. NS

Italia (Genova) N=104. CDDP+5FU+ EBRT + Cistect vs Cistect. NS

MGH/RTOG N=185. CNV+ CDDP-EBRT vs CDDP-EBRT. Pendiente

Italia (Veneto) N=182 MVAC + Cistect vs Cistect. Pendiente

Millikan et al (MDACC) (JCO 2001; 19:4005-13). T3-T4 with MVAC x 2 ->Cystectomy->MVACx3 standard: M F up 6.8y; DFS 58%; pT0 40%.

Vale C et al (Lancet 2003; 36:1927-34). Meta-analysis advanced bladder cancer studies: N=2688 in 10 trials. Neoadjuvant CDDP based combination therapy benefit OS HR=0.87, 13% reduction of death risk and 5% absolute benefit in OS at 5 y. Neoadjuvant chemotherapy is favorable even for single agent CDDP, but combination therapy is better. No significant differences for cystectomy vs EBRT vs Cystectomy + EBRT, although this shows a better trend.

C Rödel et al (JCO 2002;20:3061-71). N=415, single institution EBRT+/- ChX (salvage cystectomy if not CR): CR 72%, 10yNED 64% and 10yDistant Mets 35%; 10yDspecif Surviv 42%; 80 bladder preservation; cystectomy due to fibrosis 2%; cystectomy for recurrence 10ySpecif Survival 45%.

C Sternberg (Sem Oncol 2007;34:122-8). Adjuvant chemotherapy review (CUSCA, MVAC, CDDP, CM, CMV, MVEC) meta-analysis showed a 9% improvemente in 3 yOS . Studies with lack of power and without the best drugs...

CARCINOMA UROTELIAL METASTASICO

Factores pronostico: KPS<80 & Visceral mets: MST 0 factores 33 me; 1 factor 13.4 me; 2 factores 9.3 me.

MVAC: MTX 30 mg/m² d1, 15 & 22 + VBL 3 mg/m² d2, 15 & 22 + ADM 30 mg/m² d2+ CDDP 70 mg/m² d 2. (6yDFS 3.7%)

MVEC: MTX 30 mg/m² d 1, 15 & 22 + VBL 3 mg/m² d 2, 15 & 22 + EPI 70 mg/m² d2 + CDDP 50 mg/m² d 2.

HD MVAC: MTX 1 g/m² d1 /CF d2 + VBL 3 mg/m² d2, 15 & 22 + ADM 30 mg/m² d2+ CDDP 70 mg/m² d 2. (similar to standard dose)

MVAC q 2 wk (benefit in CR, OR and PFS but not in OS)

CDDP 25 mg/m² x 4 + 5FU/CF 800 mg/m² x 4 + MTX 60 mg/m²

CDDP 100 mg/m² d1 + MTX 30 mg/m² d 1 & 8 + VBL 4 mg/m² d 1 & 8

CBDCA 300 mg/m² d 1 + MTX + VBL

CDDP 25 mg/m² d 1, 8, 15 & 22 + 5FU 500 mg/m² x 5 d d 1-5 & 22-26 + IFNalpha2b 5 MU d 1-5 & tiwk (MVAC better)

CDDP 75 mg/m² d1 + GEM 1000 mg/m² d 1, 8 & 15 q 4 wk. (similar to MVAC)

MSKCC: ADM 50 mg/m² + GEM 2000 mg/m² qowk x 6 then IFX 1.5 g/m² x 3 + TXL 200 mg/m² + CDDP 70 mg/m² q 3 x 4 (OR 86%; CR 43%).

IFX 1.5 g/m²/d x 3d/MESNA + TXL 200 mg/m² in 3 h + CDDP 70 mg/m² d 1
Gallium N 300 mg/m²/d civi x5 + VBL 0.11 mg/kg d 1&2 + IFX 1.2 g/m² d 1-5 /MESNA.

TXL 200 mg/m² d 1 + CBDCA AUC 5 d1 + GEM 800 mg/m² d 1 & 8 q 3 wk.

Bellmunt: TXL 80 mg/m² d 1 & 8 + CDDP 70 mg/m² + GEM 1000 mg/m² d 1 & 8

ALIMTA

L Einhorn et al (Sem Oncol 2003;30:34-41). Galium nitrate 300 mg/m² qd civi x 5. Activity as a single agent OR 26% (N=73; 3 series; only prior adjuvant therapy). Combination therapy with VBL 0.11 mg/kg x 2 + IFX 1.2 g/m² x 5 in N=68, OR 39%. Combination with 5FU 1000 mg/m² civi x 5 OR 12%. Finally Randomized study of MVAC vs 5FU+Ga Nitrate (N=34) OR 94% vs 12%; MST 17 vs 19 mo.

PN Lara et al (Cancer 2004;100:82-88). N=25. TXL 100 mg/m² in 3 h + MTX 30 mg/m² + GEM 1000 mg/m² d 1 & 8 repeated q 3 wk. OR 57% (CR 23.5%); MOS 18 mo; MPFS 9.2 mo.

A Barnias et al (JCO 2004;22:220-8). N=220. Randomized TXT 75 mg/m² + CDDP 75 mg/m² + GCSF q 3 wk (OR 37.4%; MTTP 6.1 mo) vs MVAC standard + GCSF (OR 54.2%; MTTP 9.4 mo), better but more toxic.

R Dreicen et al (Cancer 2004;100:1639-45). TXL+ CBDCA (OR 28.2%; MPFS 5.2 mo; MOS 13.8 mo) vs MVAC (OR 35.9%; MPFS 8.7 mo; MOS 15.4 mo).

J Li et al Indiana Univ (JCO 2005;23:1185-91). N=36, M F up 38.7 mo. Phase II TXL 90 mg /m² + GEM 800 mg/m², both wkly d1, 8 & 15 q 4 wk. MST 15.8 mo, OR 69.4%; CR 41.7%. Pulmonary toxicity grade 3-5 in 14%.

J Hainsworth et al (Cancer 2005;103:2298-303). N=63, Phase II TXL 200 mg/m² d 1 + CBDCA AUC 5 d1 + GEM 1000 mg/m² d 1 & 8. OR 46% (CR 12%); MST 11.8 mo, 2 y OS 27%. No improvement compared to older series.

***H Van der Maase et al (JCO 2005;23:4602-8). N=405. Randomized GEM + CDDP (MST 14; 5 y OS 13%; MPFS 7.7mo; 5 yPFS 9.8%) vs MVAC (MST 15.2 mo; 5 yOS 15.3%; MPFS 8.3 mo; 5yPFS 11.3%). Prognostic factors for long term survival were KPS, M0, low Alk Phase, <3 mets sites and absence of visceral mets (withour these factors 5 yOS 20.9% vs 6.8%)

**J Garcia & R Dreicer (JCO 2006;24:5545-51). Review ChX: MVAC (OR 60%; MST 15 mo) > other including CDDP + TXL, and equal to CDDP + GEM. Alimta Phase II OR 32% + NC 36%. Target therapies: Gefitinib + CDDP + GEM = CDDP + GEM; Trastuzumab (Her2+ 53%) + TXL + CBDCA + GEM OR77%. BV + ChX (CDDP + GEM) on going. Second line: IFX, TXT, CDDP+GEM (OR 20-40%).

****C Sweeney et al (JCO 2006;24:3451-7). N=47, second line Rx. Alimta 500 mg/m² d 1 q 3 wk + Vit B12 + FA. OR (49%): 3 CR + 10 PR + 10 NC; MOS 9.6 mo; MTTP 2.9 mo; MDR 5 mo.

M Galsky et al MSKCC (Cancer 2007;109:549-55). CDDP ineligible patients due to CrCl' 30-60/ml, Cr >1.5, prior nephrectomy). DOX 50 mg/m² + GEM 2 g/m² qowk x 5 abd then TXL 65 mg/m² + CBDCA AUC 1.7 wkly x 12. N=25. OR 56% (5 CR + 9 PR); MST 15 mo; M F up 45 mo DFS 28%.

MHA Hussain et al (JCO 2007;25:2218-24). N=57/109 had Her2+ ann 44/57 underwent a Phase II study with Herceptin 4 mg/kg -> 2 mg/kg d 1, 8 & 15 + TXL 200 mg/m² d1 + CBDCA AUC 5 d 1 + GEM 800 mg/m² d 1 & 8. Results: 2 therapy related deaths ; 31/44 (70%) OR (5CR + 26PR); MTTP 9.3 mo; MOS 14.1 mo; cardiac toxicity 22.7% grade 1-3. Now proceeding to a randomized trial.

***** (ASCO 2007)*LBA 5030. Urinary bladder EORTC trial. TXL + CDDP + GEM > CDDP + GEM. RR=57.1% (CR 15%) vs 46.4% (CR 10%). MST 15.7 mo vs 12.8 mo.

(ASCO 2007)5079. Alimta 500 mg/m² + GEM 1000 mg/m² d 1 & 8 q 3 wk in urothelial bladder cancer. N=46, untreated. 1CR + 10 PR (OR 28%)+ 11 NC.

(ASCO 2007)*5080. Sunitinib in bladder cancer. N=21. 2 PR + 8 NC, in 15 evaluable...

(ASCO 2007)*5083. MDACC Small cell bladder cancer. IFX/DOX alternating with CDDP/VP. 5 yu OS 48%. Cystectomy after 4 cycles.