

Hemorrhagic Cystitis & Bladder Cancer

Prevention Strategies and Long-term Follow-up of Patients Who Receive Cyclophosphamide

Benjamin K. Canales MD, MPH
Assistant Professor, Department of Urology
University of Florida
benjamin.canales@urology.ufl.edu

ASN, November 18, 2010



Disclosure

- No financial disclosures
- No conflict of interest
- Off-label drug and dosing protocols will be discussed.



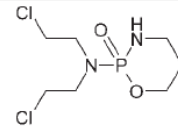
Outline - CYC

- **Hemorrhagic Cystitis/Bladder Cancer**
- Prevention Strategies/Effectiveness
 - IVF/Mesna protocols
- Management of Other Complications
 - BK Virus
 - Stepwise hematuria interventions



UF Department of Urology
UNIVERSITY of FLORIDA

Cyclophosphamide (CYC)



- N,N-bis(2-chloroethyl) tetrahydro-2H-1,3,2-oxphosphorin-2-amine, 2-oxide monohydrate
- Family: Oxazaphosphorine alkylating agent
- Generics: Endoxan, Cytosar, Neosar, Procytox, Revimmune
- Potent immunosuppressant

UF Department of Urology
UNIVERSITY of FLORIDA

CYC Clinical Uses

- **Cancer**
 - Solid: ovarian ca, lung Ca, neuroblastoma
 - Hematologic: lymphomas, leukemia, multiple myeloma
- **Non-neoplastic autoimmune diseases**
 - Systemic vasculitis: Wegener's, PAN, Lupus
 - Rheumatoid arthritis
 - Multiple sclerosis
- **Renal**
 - Minimal change disease (resistant)
 - Lupus nephritis
 - Glomerular nephritis
- **Other:** Chronic hepatitis, organ transplant, bladder cancer

CYC Administration

- **IV: 100% bio-available**
 - Cancer: 1-1.5 gm/m² 1-2 q week
 - Renal/Autoimmune: 0.5-1 gm/m² 1-2 q month
- **Oral: 75-100% bio-available**
 - Renal/Autoimmune: 1-2 mg/kg/day
- 85-90% cleared hepatic → no liver dosing
- **Metabolites:** numerous cleared in urine



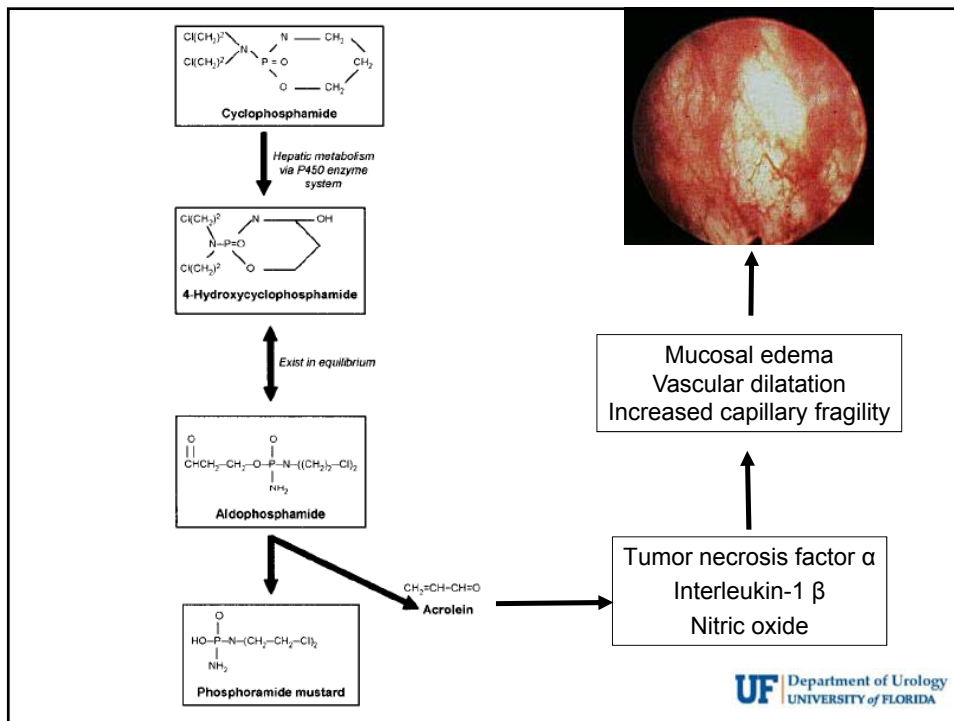
CYC Renal Dosing

Algorithm for adjusting cyclophosphamide (CYC) dose*

Creatinine clearance (mL/minute)	CYC dose (mg/kg/day)
> 100	2.0
50-99	1.5
25-49	1.2
15-24	1.0
< 15 or on dialysis	0.8

Regan *et al.* Rheum Dis Clin North Am 27, 2001

UF Department of Urology
UNIVERSITY of FLORIDA



CYC Hematuria

- Dose-dependent: 2 days → 2 years
- No standard definition
- Microhematuria: 7-53%
- Gross hematuria: 0.6 – 15%
 - Transfusion: 3/69 (4%)
 - Cystoscopy/procedures: ~1%
- Cystoscopy confirmed: 11-45%
 - Glomerular and urinary tract causes ruled out



Stillwell and Benson. *Cancer* 61, 1988; Monach *et al. Arthritis Rheum* 62, 2010

Hemorrhagic Cystitis and Oral CYC

Table 1. Incidence of hemorrhagic cystitis following treatment with daily oral cyclophosphamide (CYC)*

Author, year (ref.)	Disease(s)	CYC dose	Mesna	No. of patients		Total CYC dose, gm‡		CYC duration, months‡	
				Total	Cystitis†	Mean	Range	Mean	Range
Aptekar et al, 1973 (37)	SLE, WG, RA	1.3–1.5 mg/kg	No	46	10	28	6–74	15	3–41
Townes et al, 1976 (39)	RA	2 mg/kg	No	24	4	26	19–34	7	5–9
Plotz et al, 1979 (35)§	SLE, RA	1–4 mg/kg	No	54	7	48	2–152	28	1–91
Austin et al/Carette et al, 1986/1983 (1/36)	SLE	1–4 mg/kg	No	40	6	ND	ND	ND	ND
Stillwell et al, 1988 (32)	WG	1–2 mg/kg	No	111	17/45¶	101	5–531	38	4–144
Pederson-Bjergaard et al, 1988 (10)	NHL	100 mg/m ²	No	471	33#	ND	ND	ND	ND
Silver et al, 1993 (31)	SSc	1–2 mg/kg	No	14	2	ND	ND	9	6–12
Radis et al, 1995 (38)§	RA	50–150 mg	No	119	14	53	ND	32	ND
Talar-Williams et al, 1996 (33)	WG	2 mg/kg	No	145	42/51**	124	ND	37	ND
Reinhold-Keller et al, 2000 (34)	WG	2 mg/kg	Yes	142	17††	129	42–350	29	9–77

- Patients at risk for HC
 - >100 gram total dose
 - >30 months duration

Monach *et al. Arthritis Rheum* 62, 2010

Hemorrhagic Cystitis and IV CYC

Table 4. Incidence of hemorrhagic cystitis following treatment with intermittent IV cyclophosphamide (CYC) for rheumatic diseases*

Author, year (ref.)	Disease(s)	CYC dose	Mesna	No. of patients		Total CYC dose, gm		CYC duration, years	
				Total	Cystitis	Mean	Range	Mean	Range
Austin et al, 1986 (1)	SLE	0.5-1.0 gm/m ² every 3 mos	No	20	0	ND	ND	4	ND
Hoffman et al, 1990 (48)	WG	1.0 gm/m ² every 1-3 mos	No	14	1†	ND	ND	0.8	0.1-1.8
Gourley et al, 1996 (3)	SLE	0.75 gm/m ² every 1-3 mos	Yes	55	0	ND	<15	ND	<3
Martin et al, 1997 (50)	SLE, vasc	0.5-1.0 gm/m ² every mo	No	75	0	5	ND	0.5	ND
Guillemin et al, 1997 (53)	WG	0.7-1.0 gm/m ² every 3-6 wks	No	27	1	28	ND	ND	ND
Adu et al, 1997 (54)	WG, MPA, PAN	15 mg/kg every 2-6 wks	Yes	24	0	ND	<30	ND	<1.5
Martin-Suarez et al, 1997 (55)	SLE, vasc, myo	0.5 gm every 1-4 wks	Yes/no	90	1‡	3	1-25	0.3	0.0-3.7
Koldingsnes et al, 1998 (51)	WG	15 mg/kg every 2-8 wks	No	11	0	ND	12-88	3.3	1.0-8.2
Haubitz et al, 1998 (52)	WG, MPA	0.75 gm/m ² every mo × 12	No	22	0	16	<20	ND	<1
Ginzler et al, 2005 (6)	SLE	0.5-1.0 gm/m ² every mo × 6	No	69	0	ND	<9	ND	0.1-0.5
Hoyles et al, 2006 (8)	SSc	0.6 gm/m ² every mo × 6	No	22	0	6	ND	ND	0.1-0.5
Goransson et al, 2008 (49)	SLE, WG, myo	15 mg/kg every mo	No	42	0	10	1-52	1.2	0.0-8.8

- Periodic IV CYP → low risk HC

Bladder Cancer and CYC

TABLE III. Urinary Bladder Tumors in Male Sprague Dawley Rats Receiving Cyclophosphamide in Drinking Water Five Times/Day (Lifetime)

Tumor type	Dose (mg/kg/day)				
	0	0.31	0.63	1.25	2.5
Urinary bladder ^a	0/38 (0%)	2/34 (6%)	2/36 (5%)	5/35* (14%)	7/31** (23%)

- Schmahl & Habs late 1970's noted SD rats
- Confirmed late 1980's in humans

Bladder Cancer and Oral CYC

Table 2. Incidence of bladder cancer following treatment with daily oral cyclophosphamide (CYC)*

Author, year (ref.)	Disease(s)	CYC dose	No. of patients			Latency, years	OR	95% CI	CYC treatment		Followup, years‡
			Total	Bladder cancer					Duration, years	Total dose, gm†	
Aptekar et al, 1973 (37)	SLE, WG, RA	1.3-1.5 mg/kg	46	0		NA	NA	NA	NA	ND	
Plotz et al, 1979 (35)	SLE, RA	1-4 mg/kg	54	2	6-7	100	ND	2-4	ND	4.5	
Austin et al/Carette et al, 1983/1986 (1/36)	SLE	1-4 mg/kg	40	1	4	ND		4	ND	7.1	
Stillwell et al, 1988 (32)	WG	1-2 mg/kg	111	3	1-14	ND		1-12	56-531	6.0	
Pederson-Bjergaard et al, 1988 (10)	NHL	100 mg/m ²	471	7	5-12	6.8	3.2-14.2	2.8-4.2	83-129	3.8	
Radis et al, 1995 (38)	RA	50-150 mg	119	9	4-23	22	8.8-56	5‡	120 ± 56	13.1	
Talar-Williams et al, 1996 (33)	WG	2 mg/kg	145	7	0.6-15	31	13-65	0.6-5.1	19-251	8.5	
Westman et al, 1998 (40)	WG, MPA	2 mg/kg	123	3	>5	4.8	1.0-13.9	>1	ND	4.6	
Reinhold-Keller et al, 2000 (34)	WG	2 mg/kg	142	1	7	ND		6	350	7.0	
Knight et al, 2004/2002 (42,43)	WG	ND	1,065	11	4-15	4.8	2.6-8.1	7.2‡	0-234	ND	
Faurschou et al, 2008 (41)	WG	1-2 mg/kg	293	5	7-18	3.6	1.2-8.3	>1#	>36#	6.0	

- Patients at risk for bladder Ca
 - >100 gram total dose

Monach et al. Arthritis Rheum 62, 2010

UF Department of Urology
UNIVERSITY of FLORIDA

Bladder Cancer Risk after HC

Table 3. Association of bladder cancer with a prior diagnosis of hemorrhagic cystitis in patients treated with daily oral cyclophosphamide*

Author, year (ref.)/ cystitis definition	Disease	Bladder cancer		No bladder cancer		P†
		Cystitis	No cystitis	Cystitis	No cystitis	
Stillwell et al, 1988 (32) Cystoscopy	WG	3	0	14	94	0.003
Pedersen-Bjergaard et al, 1988 (10) No data	NHL	2	5	31	433	0.08
Radis et al, 1995 (38) Nonglomerular hematuria	RA	5	4	13	97	0.004
Cystoscopy		3	6	11	99	0.07
Talar-Williams et al, 1996 (33) Nonglomerular hematuria	WG	6	1	45	93	0.008
Cystoscopy		5	2	46	92	0.10
Reinhold-Keller et al, 2000 (34) Cystoscopy	WG	1	0	16	125	0.12
Total Nonglomerular hematuria		17	10	119	842	<0.0001
Cystoscopy		14	13	118	843	<0.0001

Monach et al. Arthritis Rheum 62, 2010

UF Department of Urology
UNIVERSITY of FLORIDA

Bladder Cancer and IV CYC

- Case reports only for pulse regimens
- Multi-center cohort study
 - 9,547 lupus patients followed for 8 years
 - Bladder cancer OR 1.23 (95% CI 0.66-2.11)
 - Assumed at least 30% of patients received pulsed IV CYC for at least 6 month duration
- Risk higher in oncology patients receiving high-dose CYC and ifosfamide (10-20%)

Bernatsky *et al.* Arthritis Rheum 52, 2005

UF Department of Urology
UNIVERSITY of FLORIDA

Bladder Cancer Screening?

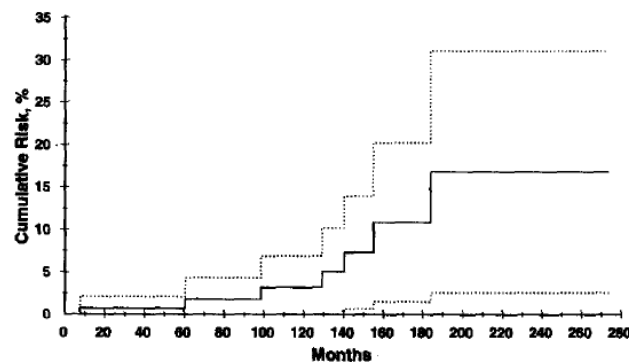


Figure 3. Cumulative risk for bladder cancer in 145 patients treated with cyclophosphamide who had Wegener granulomatosis; time from first cyclophosphamide dose to development of bladder cancer. Dashed lines represent 95% CIs.

Talar-Williams *et al.* Ann Intern Med 124, 1996

UF Department of Urology
UNIVERSITY of FLORIDA

Bladder Cancer Screening?

- *Lifelong surveillance* indicated in prolonged CYC use
 - Urinalysis/urine cytology every 6 - 12 months
 - No cytology studies exist in post-CYC setting
- Refer to urology for hematuria work-up if:
 - New onset non-glomerular microhematuria
 - Gross hematuria
- Consider repeating every 1-2 years for:
 - Patients with endoscopic bladder changes
 - Hemorrhagic cystitis by history
 - High risk due to concomitant tobacco use

Talar-Williams *et al.* Ann Intern Med 124, 1996

UF Department of Urology
UNIVERSITY of FLORIDA

CYC Urinary Risk Summary

- Hemorrhagic cystitis – 35% patients
 - Oral > IV
 - Cumulative higher dose (100 gm)
 - Longer duration (30 months)
- Bladder cancer → high risk need surveillance
 - Long-term oral regimens (5-15%)
 - High-dose oncology regimens (10-20%)
 - HC *may* be associated with future risk
 - TCC may occur 15 years after CYC

UF Department of Urology
UNIVERSITY of FLORIDA

Outline - CYC

- Hemorrhagic Cystitis/Bladder Cancer
- **Prevention Strategies/Effectiveness**
 - IVF/Mesna protocols
- Management of Other Complications
 - BK Virus
 - Stepwise hematuria interventions



UF Department of Urology
UNIVERSITY of FLORIDA

HC Prevention: Sensible steps

- 1) Limit dose
- 2) Intermittent oral CYC therapy
 - Interstitial nephritis*
- 3) Discontinue as soon as possible
 - Replace with a less toxic alternative



Boumpas *et al.* Lancet 340, 1992

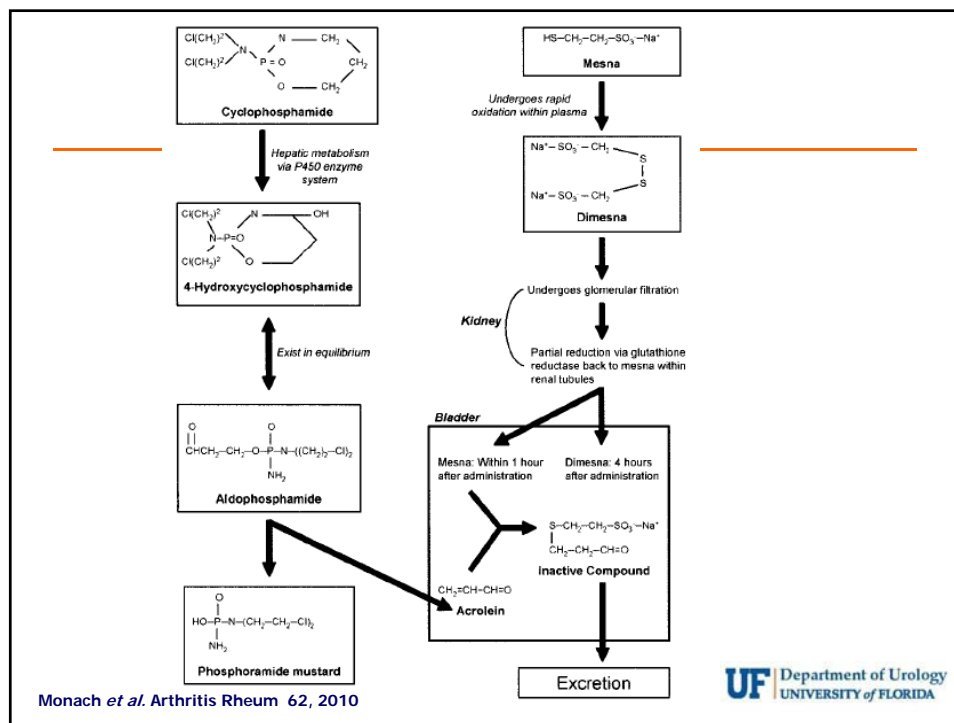
UF Department of Urology
UNIVERSITY of FLORIDA

HC Prevention: Mesna

- IV/oral form: FDA approved for HC prophylaxis during ifosfamide-containing drug regimens
- 100 µg/ml urine → “uroprotective” concentration
- IV Loading dose: 7.5 mg/kg or 300 mg/m² prior to drug tx and q4 hours x 2; \$1/daily dose
- Oral dose: 400 mg film coated; \$50/pill
- SE: bitter taste, diarrhea, and headaches

Mace *et al.* Clin Cancer Res 9, 2003

UF Department of Urology
UNIVERSITY of FLORIDA



Mesna Versus Hyperhydration for the Prevention of Cyclophosphamide-Induced Hemorrhagic Cystitis in Bone Marrow Transplantation

By John D. Shepherd, Linda E. Pringle, Michael J. Barnett, Hans-G. Klingemann, Donna E. Reece, and Gordon L. Phillips

- PRCT in 100 BMT patients
- N=51 → Mesna (160% CYC dose) and 1.5 L NS m²/day
- N=49 → 3 L NS m²/day

Table 2. Results of Urinary Prophylaxis

Degree of Hematuria*	Mesna	Hyperhydration
None	13	13
Minor	14	19
Consistent	8	5
Severe	5	3
Not assessable	3	1
Menses†	8	8

} p=0.31

Shepherd *et al.* J Clin Oncol 9, 1991

UF Department of Urology
UNIVERSITY of FLORIDA

Mesna Compared With Continuous Bladder Irrigation as Uroprotection During High-Dose Chemotherapy and Transplantation: A Randomized Trial

By Julie M. Vose, Elizabeth C. Reed, Gregory C. Pippert, James R. Anderson, Philip J. Bierman, Anne Kessinger, Jorge Spinolo, and James O. Armitage

- PRCT in 200 BMT patients
- N=103 → 250 ml/hr NS, Mesna (100% CYC dose)
- N=97 → 250 ml/hr NS, CBI (NS) @ 200 ml/hr

Table 2. Hematuria Incidence

	Foley Catheter (%)	Mesna (%)	P
Maximum hematuria grade			
0	24	47	.007
I	26	18	
II	32	17	
III	13	10	
IV	5	8	
Prognostic factors: grade III or IV hematuria present			
TBI-containing regimen	6	9	.91
Prior pelvic irradiation	7	10	.26
Low-dose cyclophosphamide	8	13	.21
High-dose cyclophosphamide	7	7	.97
Allogeneic transplant	14	31	.27
Autologous transplant	6	6	.96

} No difference

Abbreviation: TBI, total-body irradiation.

Vose *et al.* J Clin Oncol 11, 1993

UF Department of Urology
UNIVERSITY of FLORIDA

Continuous bladder irrigation prevents hemorrhagic cystitis after allogeneic hematopoietic cell transplantation²⁷

Molouk Hadjibabaie, Pharm.D.^{a,*}, Kamran Alimoghaddam, M.D.^b,
 Ahmad Reza Shamshiri, M.D.^c, Masoud Irvani, M.D.^b, Babak Bahar, M.D.^b,
 Asadollah Mousavi, M.D.^b, Mohammad Jahani, M.D.^b, Ali Khodabandeh, M.D.^b,
 Yasha Anvari, Pharm.D.^a, Kheirollah Gholami, Pharm.D.^a, Ardeshir Ghavamzadeh, M.D.^b

- Prospective non-randomized controlled clinical study
- N=80 → Mesna (140% CYC dose), “vigorous hydration with IVF alkalization,” and CBI (NS) @ 300 ml/hr
- N=40 → Historical controls

Comparison of outcomes of patients in the 2 groups

	Continuous bladder irrigation		P value
	Yes	No	
Incidence of hemorrhagic cystitis	13 (32.5)	20 (50)	0.11
Mean duration of hospitalization ± SD (days)	30.2 ± 9.2	39.7 ± 13.3	<0.001
Mean duration of hemorrhagic cystitis ± SD (days)	10 ± 5.4	18 ± 12.3	0.02
Mean onset of hemorrhagic cystitis (days)	8.5 ± 11.9	31.2 ± 23.8	0.001
Incidence of CMV infection	10 (25)	13 (32.5)	0.46
Incidence of UTI	13 (32.5)	8 (20)	0.20

Hadjibabaie *et al.* Urol Oncol 26, 2008



Other Therapies



- **Rats**
 - Hader JE, Marzella L, Myers RA, Jacob SC, Naslund MJ. **Hyperbaric oxygen treatment** for experimental cyclophosphamide- induced hemorrhagic cystitis. J Urol 1993;149:1617-21.
 - Vieira MM, Brito GA, Belarmino-Filho JN, Macedo FY, Nery EA, Cunha FQ, *et al.* Use **dexamethasone** with mesna for the prevention of ifosfamide induced hemorrhagic cystitis. Int J Urol 2003;10:595-602.
- **Mice**
 - Batista CK, Mota JM, Souza ML, Leitao BT, Souza MH, Brito GA, *et al.* **Amifostine and glutathione** prevent ifosfamide and acrolein-induced hemorrhagic cystitis. Cancer Chemother Pharmacol 2007;59:71-7.
 - Assrey AM, Martins GJ, Moreira ME, Brito GAC, Cavada BS, Ribeiro RA, *et al.* Prevention of cyclophosphamide induced hemorrhagic cystitis by a **glucose-mannose binding plant lectin**. J Urol 1999;10:1988-93.



Outline - CYC

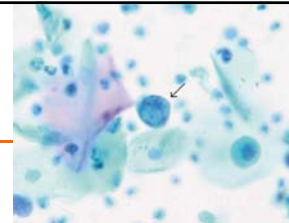
- Hemorrhagic Cystitis/Bladder Cancer
- Prevention Strategies/Effectiveness
 - IVF/Mesna protocols
- **Management of Other Complications**
 - **BK Virus**
 - **Stepwise hematuria interventions**



UF Department of Urology
UNIVERSITY of FLORIDA

BK Virus

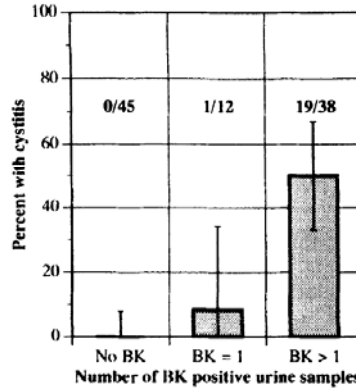
- Human polyoma virus discovered in 1971
- Exposure occurs @ age 4-5, establishes latency in GU tract
- Viral reactivation during immune compromise
 - BK nephropathy: 5% renal transplant patients
 - HC: 5.7% to 7.7% BMT recipients @ 1-4 months after tx
- Dx: RT PCR → quantification of viral load
- Tx: Cidofovir (no drug is licensed for use in polyoma virus), Leflunomide (BK nephropathy), quinolones (prophylactic)



Association of BK Virus With Failure of Prophylaxis Against Hemorrhagic Cystitis Following Bone Marrow Transplantation

By Atul Bedi, Carole B. Miller, Janet L. Hanson, Steven Goodman, Richard F. Ambinder, Patricia Charache, Ray R. Arthur, and Richard J. Jones

- PRCT in 147 BMT patients
- N=71: Mesna (120% CYC dose), NS @ 2 ml/kg/hr
- N=76: NS @ 4 ml/kg/hr, IVF and lasix titrated based on urine



Bedi *et al.* J Clin Oncol 13, 1995

UF Department of Urology
UNIVERSITY of FLORIDA

PROSTAGLANDIN E2 BLADDER INSTILLATION FOR THE TREATMENT OF HEMORRHAGIC CYSTITIS AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION

Daniele Laszlo, Alberto Bosi, Stefano Guidi, Riccardo Saccardi, Alessandro M. Vannucchi, Letizia Lombardini, Giovanni Longo, Rosa Fanci, Alberta Azzi*, Riccardo De Santis*, Pierluigi Rossi Ferrini

- Case series: 10 consecutive BMT with BK virus HC
- PGE2 (Dinoprostone) 0.75 mg in 200 ml/NS → bladder infusion, catheter clamped x 4 hours, repeated x 4 days

Table 2. Treatment with PGE2: results.

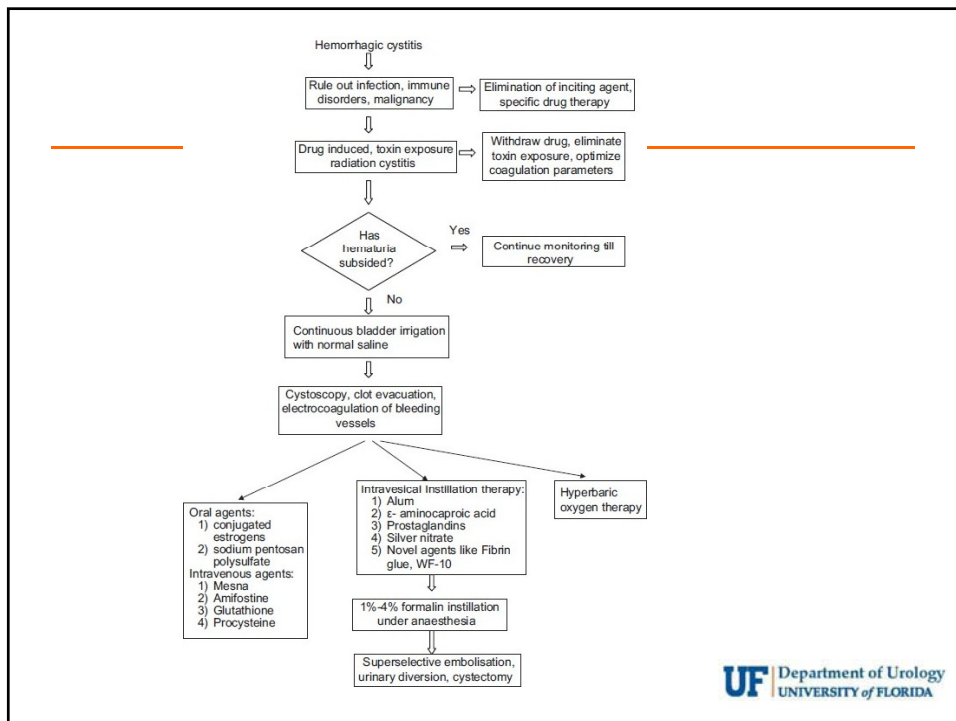
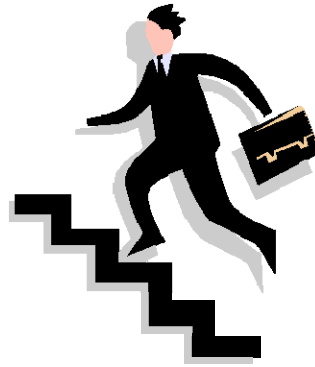
IPN	Day of onset of HC	Grade	Day of PGE2 start	Resolution of HC
74	+23	II	+23	+25
88	+56	III	+67	+69
96	+71	II	+76	+83
151	+41	I	+41	+43
152	+21	II	+26	+31
155	+27	II	+29	+37
171	+23	I	+23	+25
180	-2	I	-1	+1
183	+15	II	+16	+27
188	+24/+32	II	+24/+35	+29/+40

Laszlo *et al.* Haematologica 80, 1995

UF Department of Urology
UNIVERSITY of FLORIDA

Stepwise Interventions for Intractable Hematuria

- Prevention/Hydration
- Foley/CBI
- Cystoscopy
- Installation therapies
- Radiological embolization
- Surgical urinary diversion



Thank you for your attention!