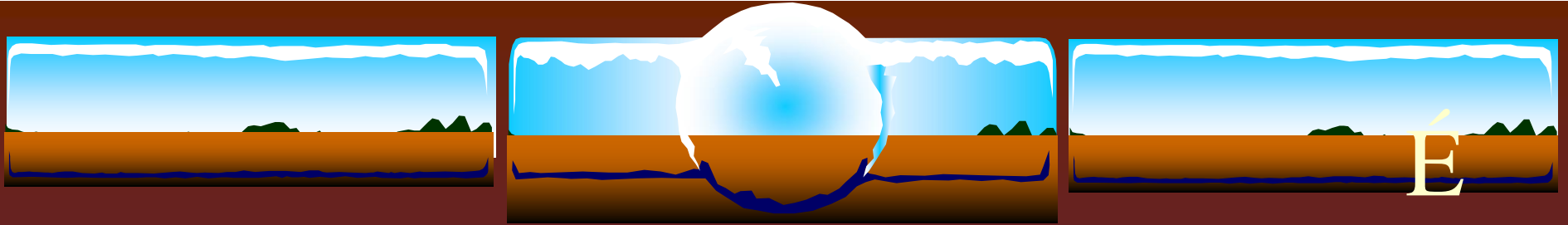


# Intravesical Chemotherapy

Jonathan Borwell



Silver Nitrate

Trichloroacetic acid

Podophyllin

Thiotepa (Jones and Swinney, Lancet, 1961)

Doxorubicin

Epirubicin (derivative from Doxorubicin)

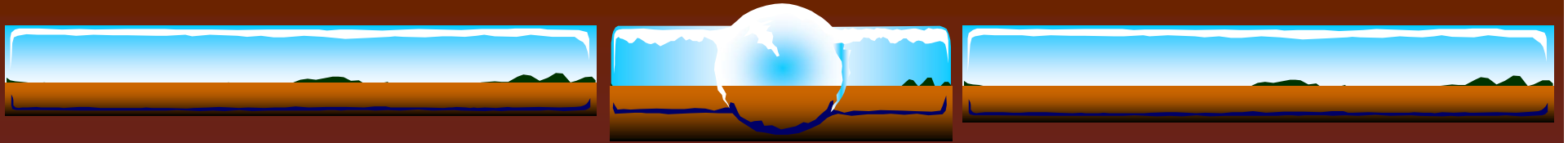
Mitomycin-C

Bacillus Calmette and Guerin

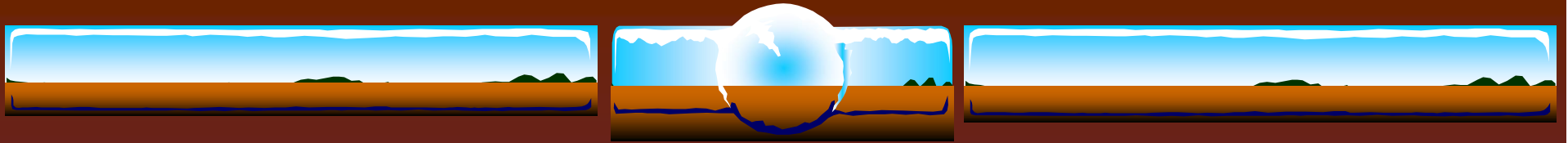


# Overview

- ❖ MMC isolated from bacterium in 1956  
(*Streptomyces Caespitosus*)
- ❖ Antibacterial and antitumoral antibiotic
- ❖ Developed as a cytotoxic agent in Japan in 1960s
- ❖ Widely used since 1962

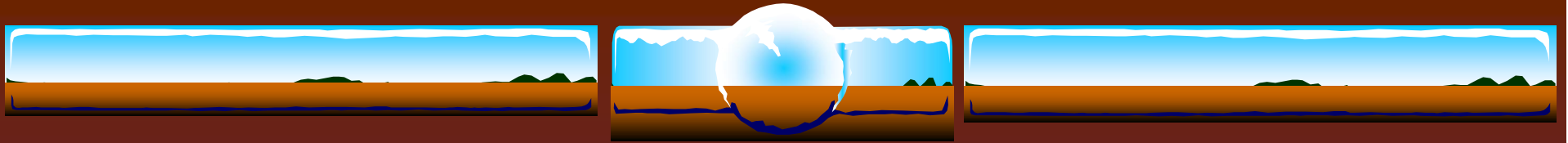


- ❖ Advanced disease
- ❖ Adjuvant therapy prior to surgery/DXT
- ❖ Metastatic breast cancer
- ❖ SCC cervix
- ❖ Head & Neck
- ❖ Colorectal + Upper GI



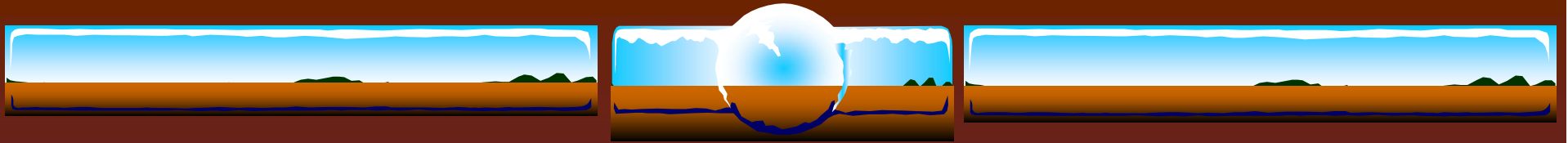
# Intravesical Mitomycin-C

- ❖ First introduced as an intravesical product in 1967
- ❖ Harrison et al (1983) reported first pilot study
- ❖ Treats residual TCC after resection and reduce tumour seed reimplantation
- ❖ Reduce recurrence and increase disease free interval



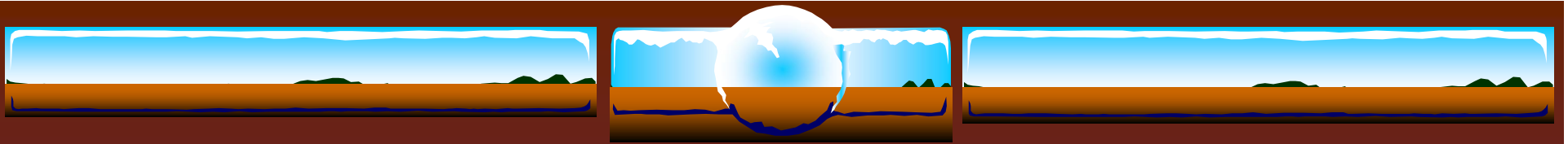
Harrison et al. Br J Urol. 1983  
Dec;55(6):676-9

- ❖ Phase II Study
- ❖ 23 pts with confirmed SBC
- ❖ 20mg in 20mls Water X3/week for 7/52
- ❖ 17/23 had total response
- ❖ 4/23 had partial response
  
- ❖ 8/23 toxic effect (incl. TCP (1); skin rash)

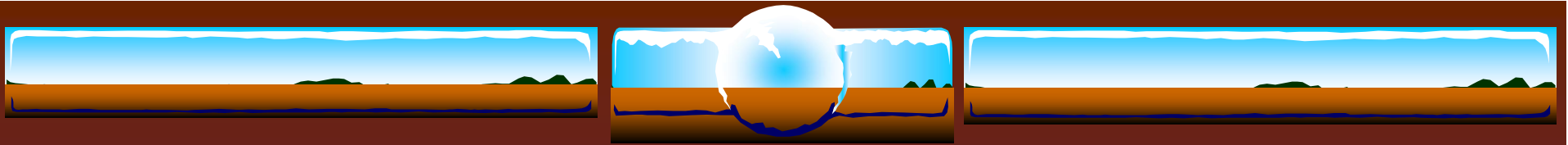


## Modality of action

- ❖ Uptake by epithelial cells.
- ❖ Activated into an alkylating agent which binds to form cross linkage with DNA and RNA  
(via a multi-step process!)
- ❖ Inhibits division of cancerous cells by blocking synthesis of DNA and RNA



- ❖ High molecular weight (334)
- ❖ Therefore low risk of systemic absorption and hence myelosuppression is rare (0.7%)

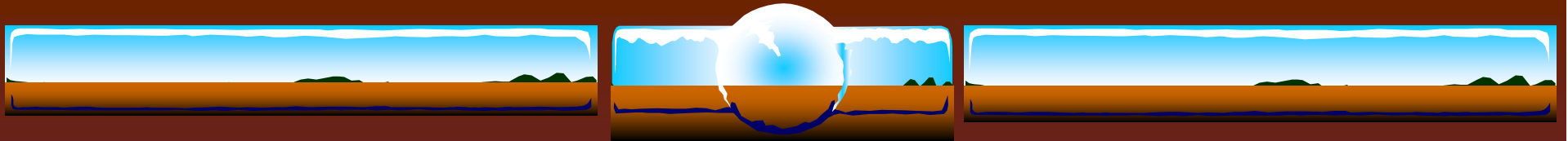


❖ Exposure advantage associated with bladder instillation ó ñinsignificant amounts of drug detected systemically.ö

Dalton et al., Cancer Res.,1991,51(19),5144-5152

Van Oosterom et al.,Controll. Clin Trials Urol.

Oncol.,1984,281-284

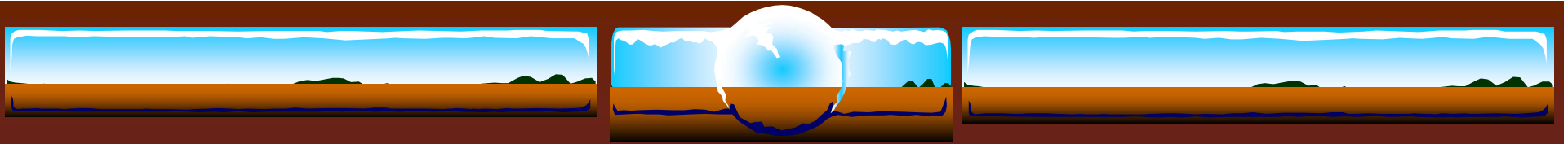


# Morbidity of treatment

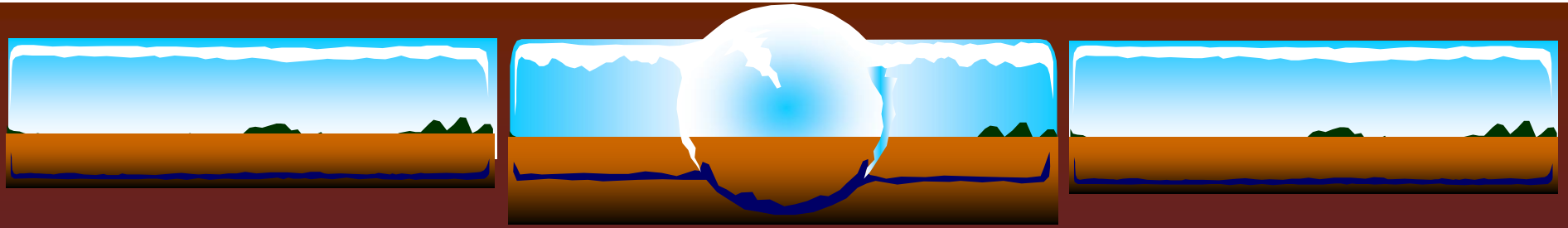
- ❖ Chemical cystitis
- ❖ UTI
- ❖ Dysuria + Frequency
- ❖ Macroscopic Haematuria
- ❖ Rash (esp. hands + groin)
- ❖ Systemic side effects incl. Thrombocytopenia + Leucopenia (delayed + cumulative) ó although more related to IV administration.



	<b>Vegt et al (1995) 30mg/50mls</b>	<b>Maffezzini et al (1995) 40mg/40mls</b>	<b>Minervini et al (1996) 30mg/?vol</b>
UTI	18.2%		
Chemical Cystitis	17.6%	16.1%	28%
Allergic Reactions	4.7%		
Local side effects	4.7%		11%
Systemic side effects	4.1%		4%

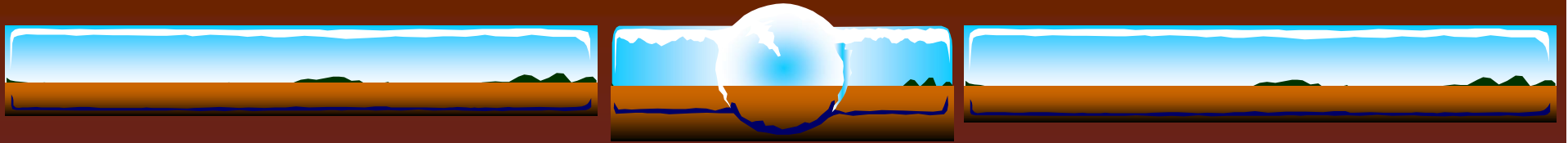


- ❖ Vegt PDJ et al., J Urol., 1995, 153:929-933
- ❖ Maffezzini M et al., Tumori., 1995, 81:191-193
- ❖ Minervini R et al., J Chemotherapy., 1996, 8: Supp 2:5-7



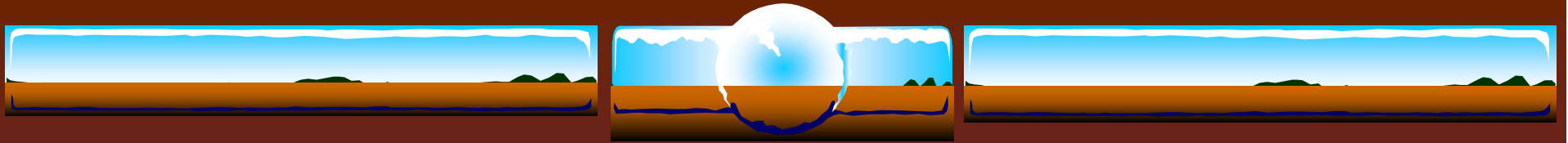
# Post-Operative IVC

The role of single-shot Chemotherapy

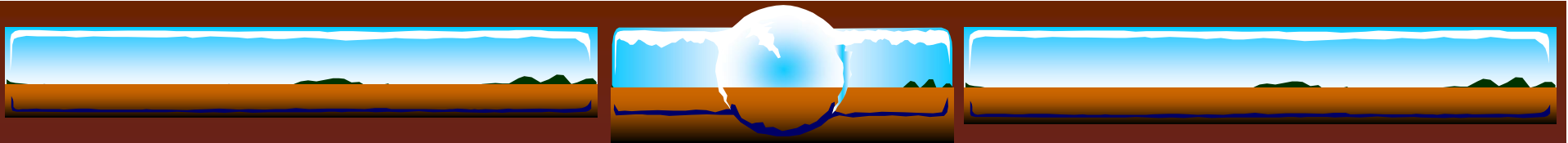


# NICE Guidelines, 2002

- ❖ "Improving Outcomes in Urological Cancers."
- ❖ The manual of cancer standards.
- ❖ Recommend a timely instillation of chemotherapy post-resection.
- ❖ [www.nice.org.uk](http://www.nice.org.uk)
- ❖ [www.doh.gov.uk/cancer/cancerplan.html](http://www.doh.gov.uk/cancer/cancerplan.html)



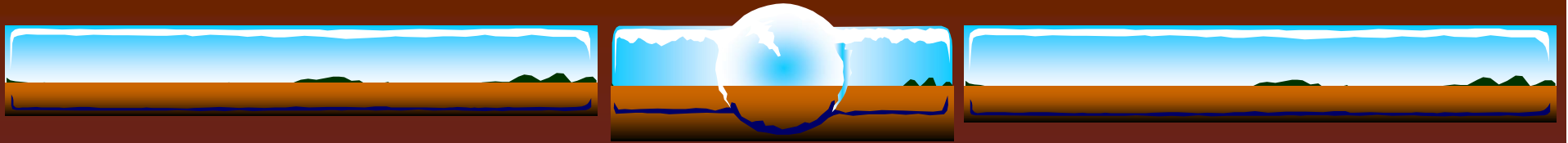
- ❖ A single dose of intravesical chemotherapy should be given within 24h of TUR(BT), unless contraindicated.
- ❖ Ideally, within 6 hours of resection (Kaasinen,2002)
- ❖ This may reduce recurrence by up to 50% for up to 2 years after treatment.
- ❖ For intermediate risk group (Multifocal,G1/G2 Ta-T1) may reduce need for further treatment.  
(Boufioux et al 1995: Tolley et al 1996)
- ❖ EAU Guidelines, 2006 + 2008



- ❖ Should be advocated for all patients after TUR(BT)
- ❖ New presentation and recurrent disease
- ❖ Multifocal disease ó 1 shot ñnot adequateö (Kaasinen; Huncharek ; EAU guidelines)



	2002	2003	2008
N	38	39	100
Exclusions	2	1	5
Male	30	26	67
Female	6	12	28
Age (years)	72.4	71.3	67.3
Histology	G1 pTa ó G3 pT2	G1 pTa ó G3 pT2	G1 pTa ó G3 pT2
Instillation time <a>	35h 54m	5h 6m	4h 9m

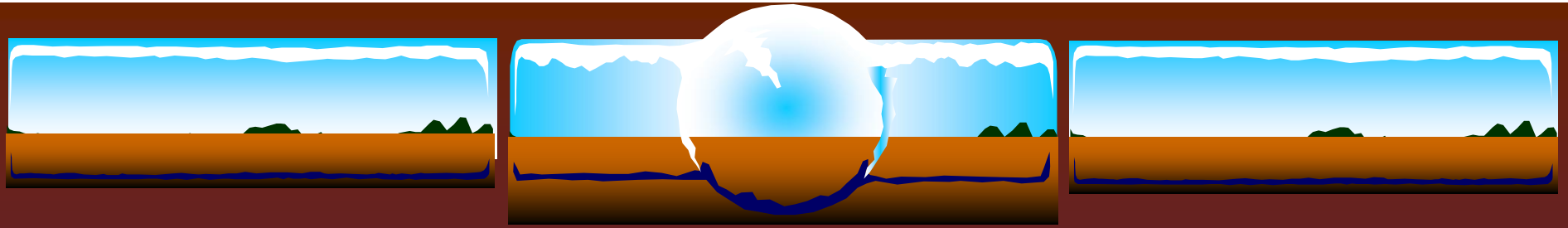


# Contraindications

- ❖ Excessive haematuria
- ❖ Risk of perforation, peri-operatively
- ❖ Reported cases of extravasation requiring surgical debridement

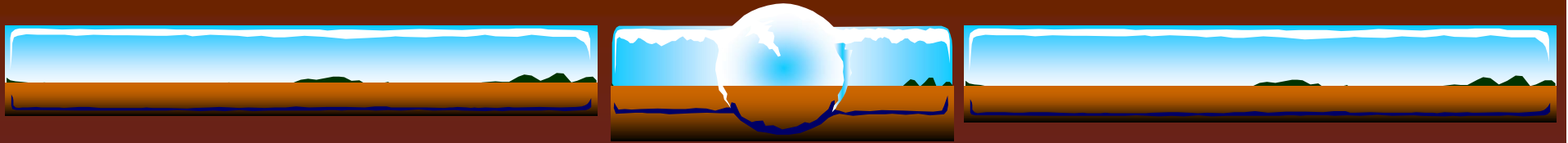
Nieuwenhuijzen et al., Eur Urol 2003;43(6):711-2

- ❖ Previous reaction to Mitomycin

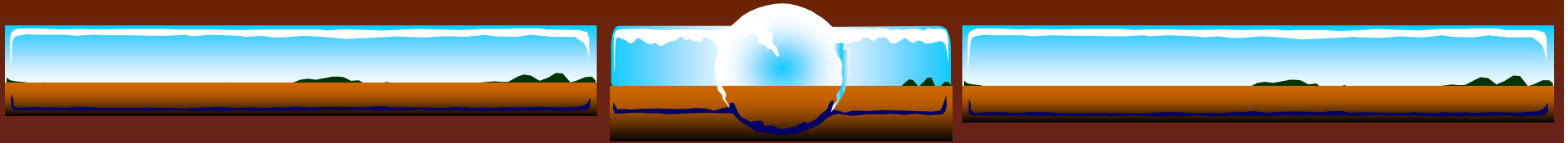


# Intravesical Chemotherapy

The role of a course of treatment

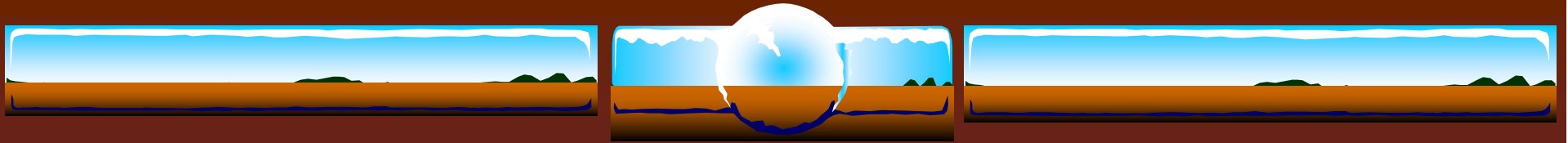


- ❖ Multifocal, superficial TCC (G1/2 Ta/T1) at initial presentation
- ❖ Recurrent superficial TCC, despite resection.
- ❖ Normally 6 doses; once weekly for 6 weeks.
- ❖ Generally, well tolerated but not without risk.



# Maintenance treatments?

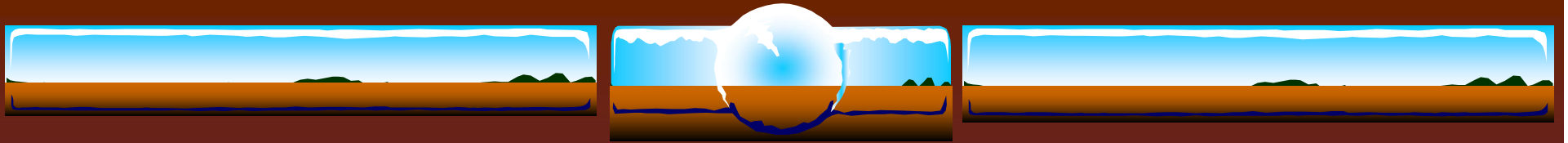
- ❖ Role not clearly defined
- ❖ Interesting paper ó Friedrich defines role of maintenance regime



# Treating Upper Tract TCC

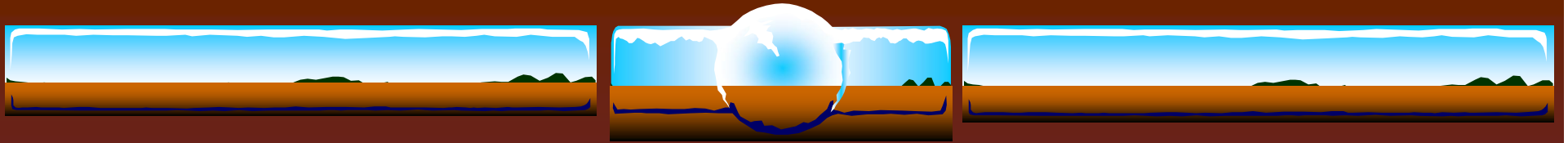
- ❖ Laser ablation of upper tract TCC.
- ❖ Insertion of ureteral and urethral catheter peri-operatively
- ❖ 40mg MMC in 3 divided doses repeated at 90 minute intervals via ureteral catheter, clamped for 30 minutes and then allowed to drain by gravity.

(Based on Keeley FX, Bagley DH, 1997. J Urol:158(6):2074-7)



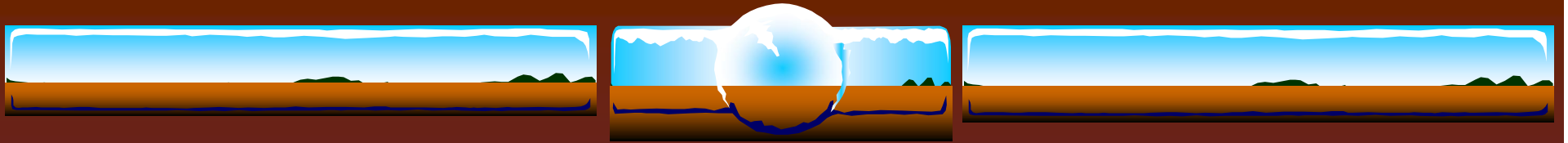
# Improving efficacy

- ❖ Urine pH (?Na Bicarbonate)
- ❖ Dehydration
- ❖ Instillation time
- ❖ Drug Concentration
- ❖ Diluent e.g. NaCl or Water



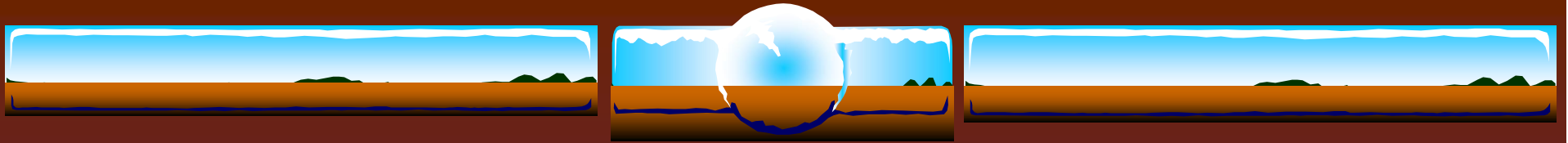
# Alternative methods of administration

- ❖ Upper tracts
- ❖ Urethral



# Upper Tract Instillation

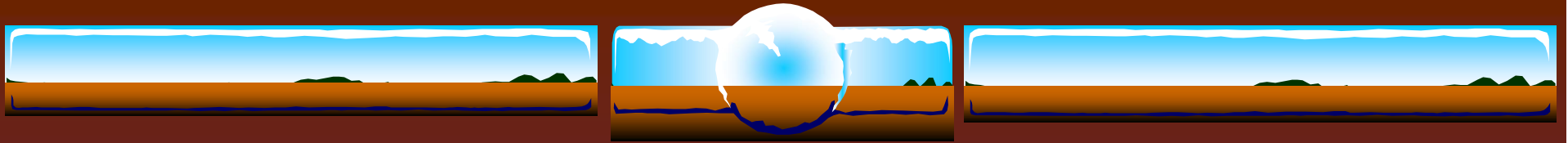
- ❖ Few studies, with limited numbers
- ❖ Nephroureterectomy should be considered
- ❖ Generally well tolerated and efficacious
- ❖ No single MMC vs BCG study



## Ideally via JJ stent/ ureteral catheter

- ❖ 6Fr Stamey catheter to renal pelvis and attached to urethral catheter.
- ❖ Mix MMC 40mg/40Mls.
- ❖ Instil 13mls over 2 minutes and clamp catheter for 10 minutes
- ❖ 2 Further instillations at 30 minute intervals and TWOC

Keeley, F J Urol 1997; 158:2074



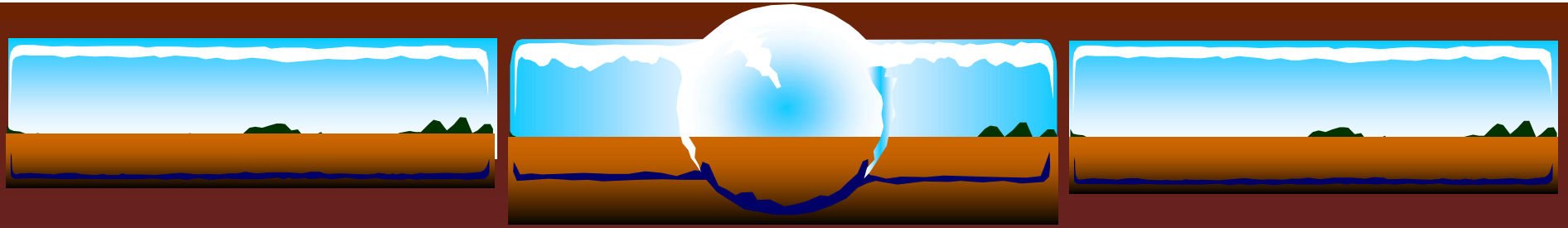
## Alternative method (used at FPH)

- ❖ Not described in literature
- ❖ 40mg/40mls MMC via ureteral catheter, instilled over 1 hour, via syringe driver and then ureteral catheter removed



# Urethral TCC

- ❖ Should consider cystoprostatectomy as an option
- ❖ NB MMC not licensed for intraurethral use
- ❖ 10mg/5mls water mixed in 10mls Lidocaine gel
- ❖ Instilled into urethra + penile clamp applied.
- ❖ Patient asked to void to expel drug
- ❖ Repeated monthly for 3/12



# Alternative Intravesical Chemotherapies



## Doxorubicin

- ❖ 50mg in 50mls of Water or 0.9% Normal Saline
- ❖ Instillation time = 1 hour
- ❖ Potential Complications ó Chemical cystitis, allergic reaction, haematuria, reduced bladder capacity, GI effects, fever.



# Epirubicin

- ❖ 50mg in 50mls 0.9% Normal Saline, dosage may be reduced where chemical cystitis experienced. Treatment for c.i.s. recommends 80mg
- ❖ Instillation time = 1 hour
- ❖ Potential Complications ó Chemical cystitis, allergic reaction. Systemic toxicity is rare.