In the name of God

HBO therapy as a rescue therapy in BK PyV -Hemorrhagic Cystitis after Allo-HSCT in children (Case presentation)

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25/2/1404

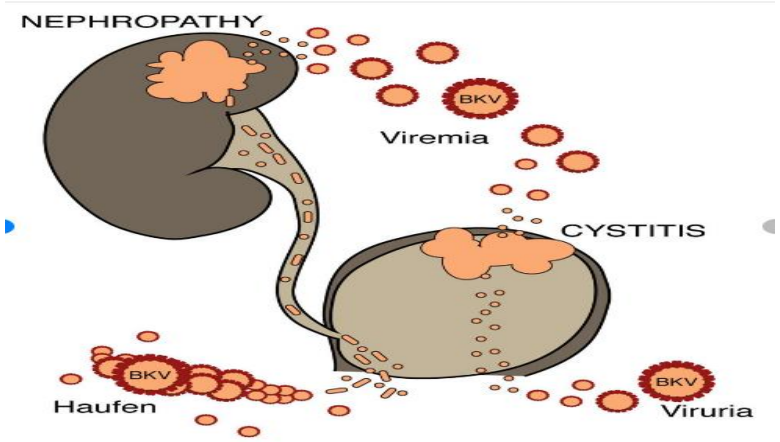
Hematopoietic stem cell transplantation (HSCT) & Hemorrhagic cystitis in children. Model for development of haemorrhagic cystitis. International Journal of Surgery 63 (2019) 34–42

- HSCT is a potentially curative treatment for many malignant and non-malignant disorders
- **FEB 2025- EBMT: Survey study (2023); 47,731 HCT in 43902 p ,by 696 European centers**
- **HSCT Complicatins; Early and Late**
- **Hemorrhagic cystitis (HC)** : one of the **most important complications** after HSCT in children, with high **morbidity & mortality**

Hemorrhagic cystitis; (BKPyV-HC; polyomaviridae -family) ,POST HSCT in Children

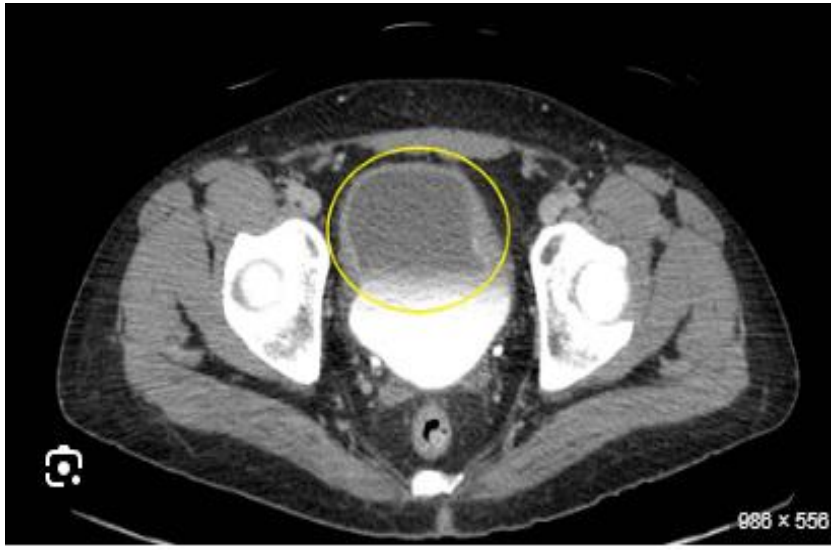
A life-threatening situation:

Impairing quality of life & Healthcare costs.

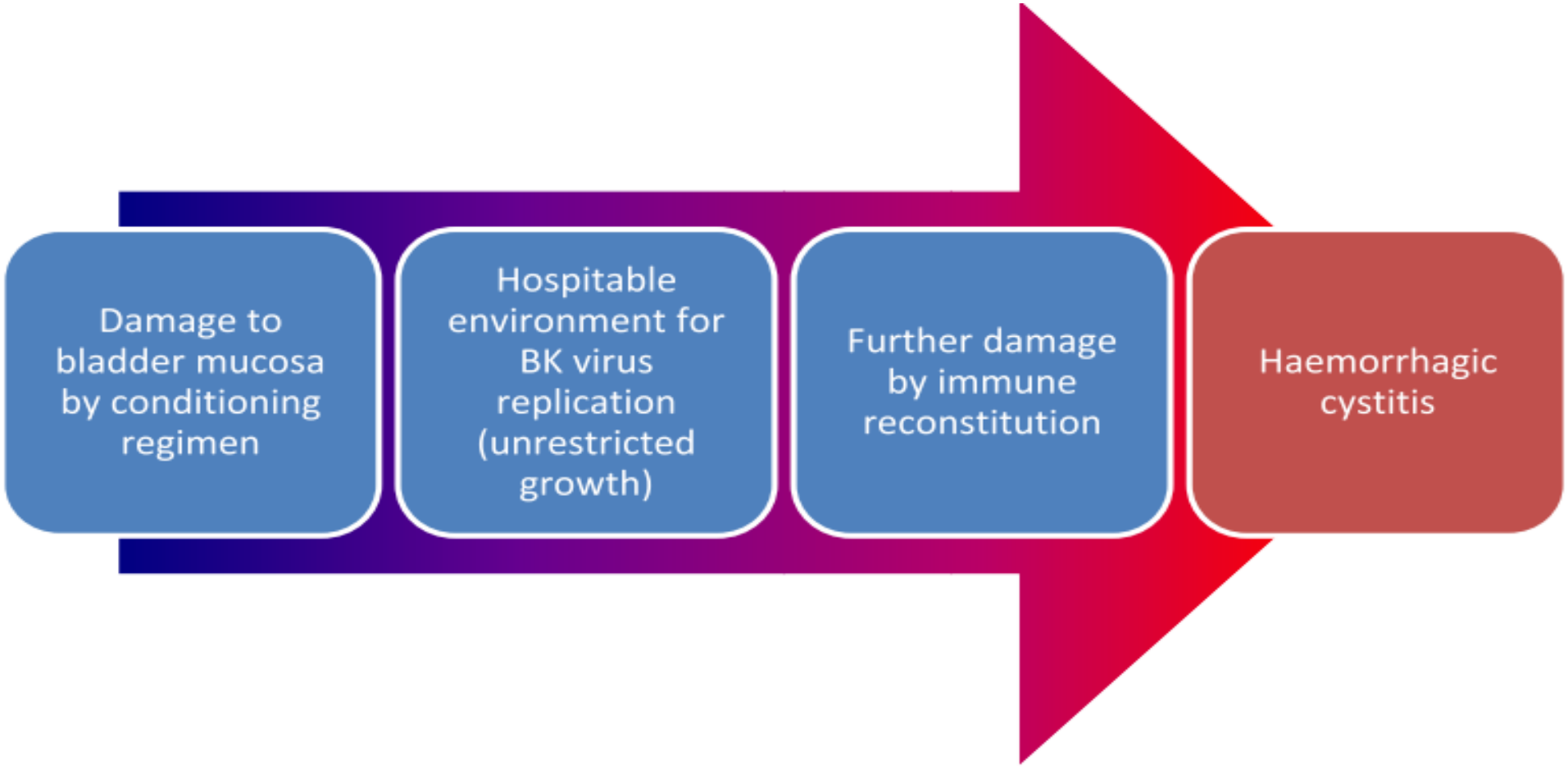


Challenges;

- Limited understanding of immunogenicity responses
- lack of proven antiviral drugs
- Side effects of available pharmacotherapy
- The need for prolonged hospitalization to manage

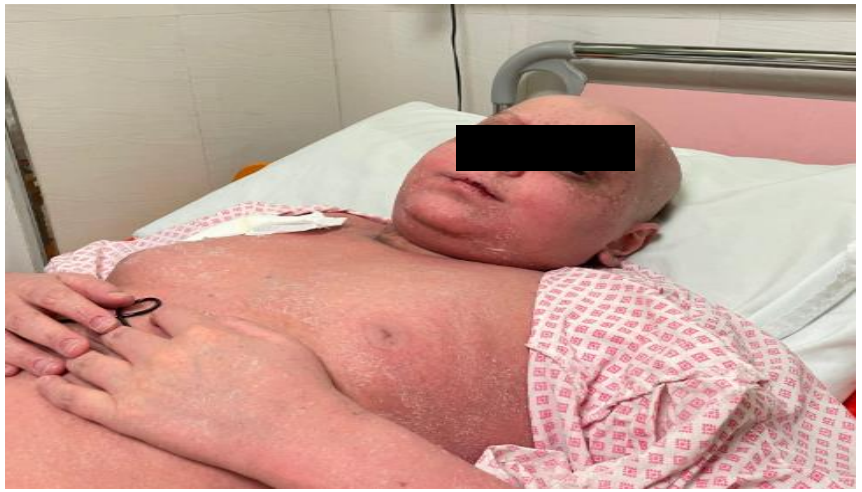


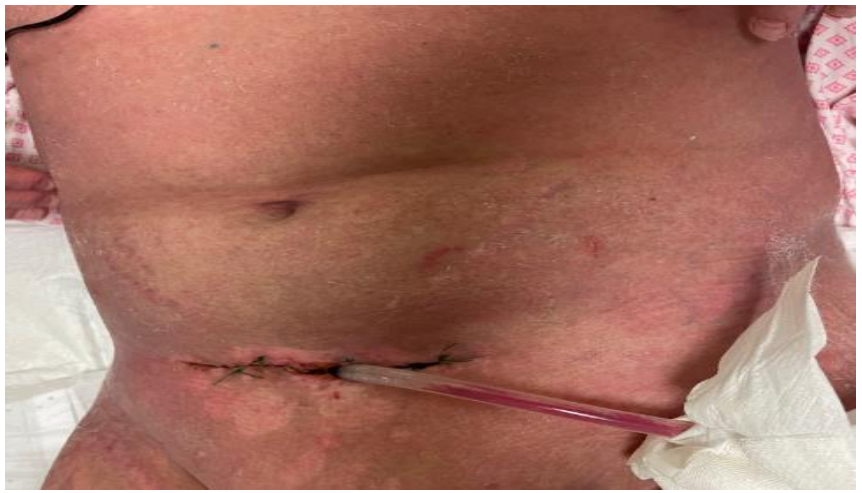
Case presentation



Case presentation: BKPy V – HC

P1; AML Non M3 , P2: ALL CNS relapse on Maintenance , P3: FA





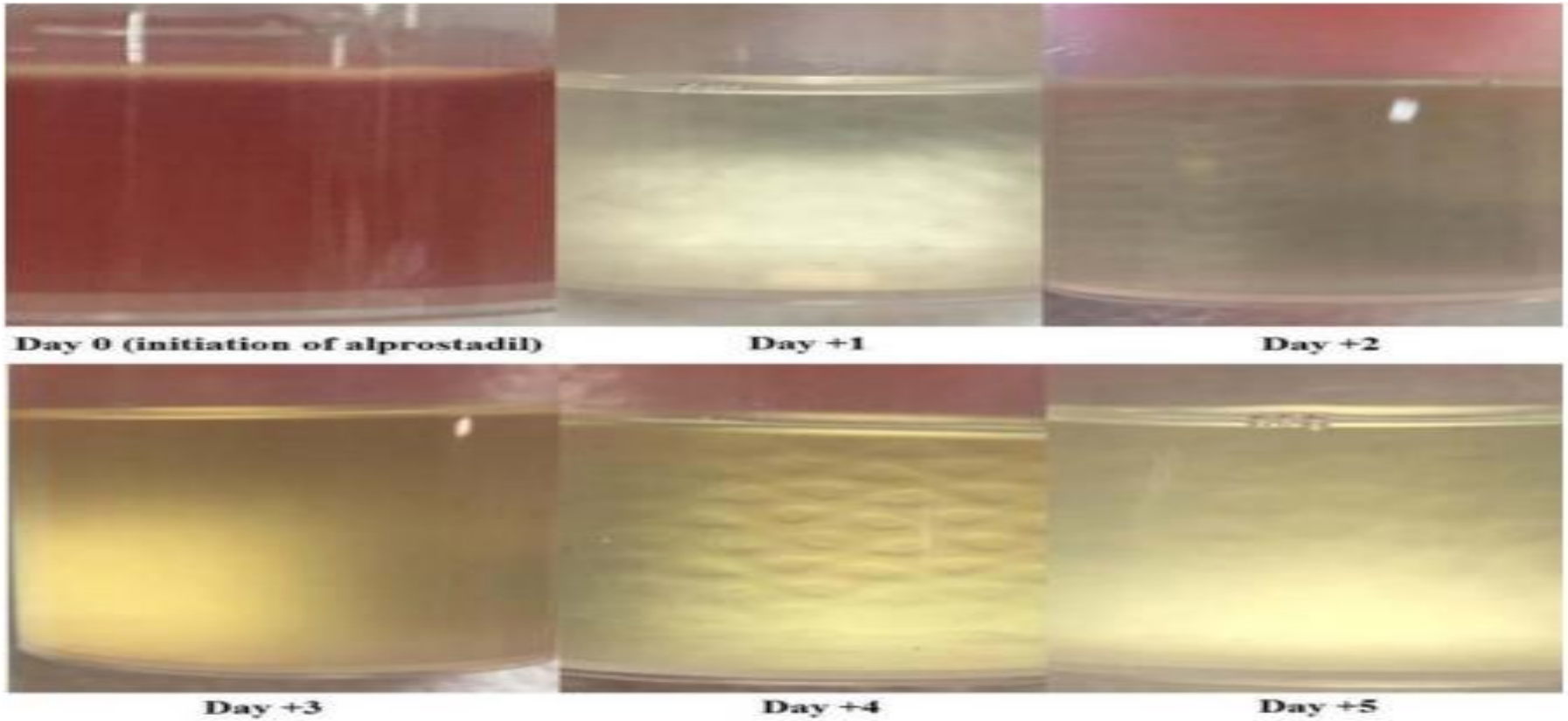
Patients	1(1398)	2(1402)	3 (1403)
Diagnosis	AML Non M3	ALL	FA
Age(Y)	13	15	10
SEX	M	M	M
Type of HSCT & Donor type	ALLO /MSD(Brother)	ALLO /MSD(Sister)	ALLO /MRD(Father)
Stem cell source	PB	PB	PB
CMV IgG (R & D)	+/+	+/+	+/+
Condition: MAC	BU + CY 50mg/kg x2D+ MEL	BU + CY 50mg /kg x 4D	CY 20mg /kg x 2D + R-ATG + FLU
GVHD -P	Cyclospurine + MTX	Cyclospurine + MTX	Cyclospurine+ MMF
Presentation	Hematuria(day +52) then ; pain , Clot, Obstruction(Grade 4)	Hematuria(Day +10) then ; pain , Clot, Obstruction(grade 4)	Hematuria(day +23) then ; pain , Clot, Obstruction (grade 4)
U/culture & Sono	Neg/ thick mucosal bladder	Neg/ thick Mucosal bladder	Neg/thick mucosal bladder

Patients	1, AML Non M3	2 ALL	3 FA
Bk Viruris (copies / ml)	107	107	107
Acute kidney failure	No	No	Yes : Creat 1.7 , transient
HC duration (Mo)	2	4	4
Complications	• CMV reactivation • Skin GVHD(Stage2) • Covid Infection; 2 times	• CMV reactivation • Skin GVHD(Stage 3)	• CMV reactivation • Skin GVHD stage 2
Treatment First line :Hyper hydration, Bladder Cath ,Analgesics , Anti Viral &platelet if plate < 50000 Reduce IS (Cipro , IVIG ???)	First line + Aryo seven + Fibrinogen…&Cystoscopy - irrigation , Intra vesicular & IV-Solutions: Alum , Hyalorinate, Alprostadil(PE1)	First line + Aryoseven + Fibrinogen…&Cystoscopy Intravesicular irrigation, IV -Solutions: Alum , Hyalorinate, Alprostadil(PE1) + HBOT	• First line + Aryoseven + Fibrinogen….&Cystoscopy – irrigation , Intra vesicular Solutions: Alum , Alprostadil (PE1)+ HBOT (partial & transient) + Embolization
Outcome	> 5 y chimerism : 100% KT & Sono : NL. U-BK:neg	Chimerism 100% U-BK:pos KT & Sono : NL. Skin GVHD : Ruxolitinib	Chimerism 100% U- Bk : pos. Sono : Mild Hydronephrosis. Creat ; 1.1- 1.2

P1- AML NON 3 Male , 13 Y :Bloody appearance of the urine

Intravesical Alprostadil ; 250 mg Alprostadil in 50 mL saline .

Good clinical responses, & stop the hematuria



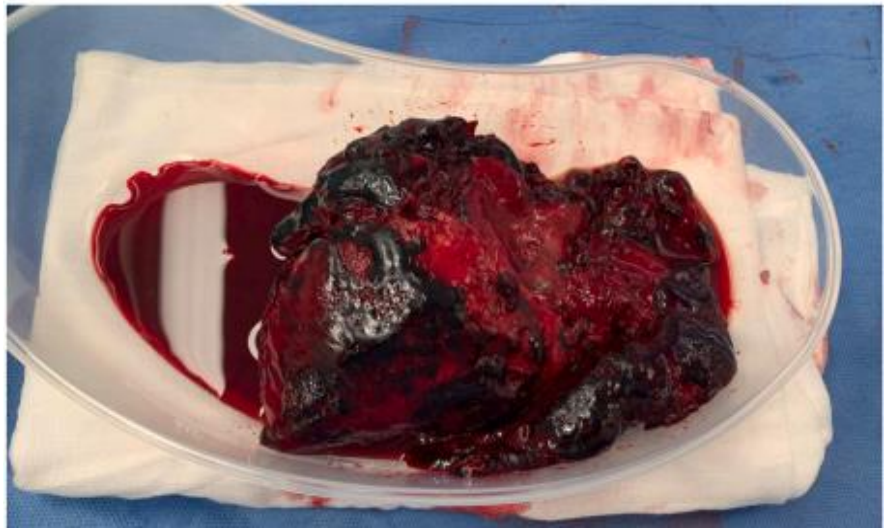
BK Hemorrhagic Cystitis ; pathophysiology

2025 EBMT:Simone Cesaro

- **HSCT : Conditioning Chemo, Radiotherapy (TBI), GVHD & immunosuppression**
- **Reactivation of BK Pyv &** Cytopathic damage of Urothelial cells , Viral shedding**(Viruria),** translocation of viruses in the blood via pretubular capillaries **(Viremia);HC**
- **Early onset (Cy- metabolit acrolein)& Late- onset(Viral ; BK , CMV , Adeno,…..)**
- **Incidence in Pediatric : 8-25%**
- **Risk Factors: Age > 7 y & Male, UR donor, Haplo HSCT , PBSC,MAC regimen , ATG,GVHD II-IV& High Virus load & Viremia>10000??**

Diffuse bladder inflammation & Vascular injury bleeding presentation ;

Symptomatic HC :25% p-BK viremia after HSCT



Grade	Symptoms
I	Non-visible haematuria
II	Macroscopic haematuria
III	Macroscopic haematuria with small clots
IV	Gross haematuria with clots causing urinary tract obstruction requiring instrumentation for clot evacuation

Haemorrhagic cystitis (HC) grading

Grade	Manifestations
0	No haematuria, no irritative symptoms
I	Non-visible (microscopic) haematuria, dysuria
II	Macroscopic haematuria
III	Macroscopic haematuria with small clots
IV	Gross haematuria with clots causing urinary tract obstruction requiring instrumentation for clot evacuation

Management Of BKv HC

EBMT Apr 2025 : Simone Cesaro

- **No approved treatment by FDA & EMA**
- **Every medical treatment: off label**

Recommended management of BKV – HC
EBMT APR 2025 : Simone Cesaro

Therapy of early onset HC

- **Hyperhydration** 3L/m2 NS (-12 to + 24 hrs from HD-Cy)
- Mesna 100-130% of Cy dose (-1hr to 24-30 hrs from HD-Cy)
- Forced diuresis
- **Analgesics** (morphine), antispasmodics (oxybutinine, tolterodine)
- **Higher threshold for PLT transfusion** (> 30-50 x 10^9/L
- Bladder catheterization (if intravesical clots) and NS irrigation

Therapy of late onset HC

- **Hyperhydration 3L/m2 NS**
- Bladder catheterization (if intravesical clots) and NS irrigation
- **Analgesics** (morphine), antispasmodics (oxybutinine, tolterodine)
- **Antiviral direct therapy (cidofovir)**
- **Reduce Immunosuppression**

Rescue

- Hyperbaric oxygen therapy (HOT)
- Cystoscopy with fibrin glue or PLT-rich-plasma application
- Intravesical CDV
- Intravesical Hyalurinic acid
- Bladder arterial embolization
- Invasive surgery (cystotomy, cystectomy)

Dell'Orso et al. Bone Marrow Transpl 2024;
Cesaro et al J Antimicrob Chemotherap 2018

Intravesical application of platelet-rich plasma(PRP) & Fibrin glue in BKPyV-Hc

On the left, the product of centrifugation of sterile PRP; on the right, the platelet activator (10%-calcium gluconate)

DOI: 10.4081/aiua.2021.2.200

ORIGINAL PAPER

Efficacy and safety of intravesical fibrin glue instillation for management of patients with refractory hemorrhagic cystitis: 12-months results. A promising therapy for hemorrhagic cystitis

Alessandra Cassani [1], Michele Marchioni [1], Francesco Silletta [1], Carlo D'Orta [1], Giulia Primiceri [1], Ambra Rizzoli [1], Patrizia Di Gregorio [2], Sandra Verna [2], Annalisa Natale [3], Stella Santarone [3], Francesco Berardinelli [1], Luigi Schips [1]

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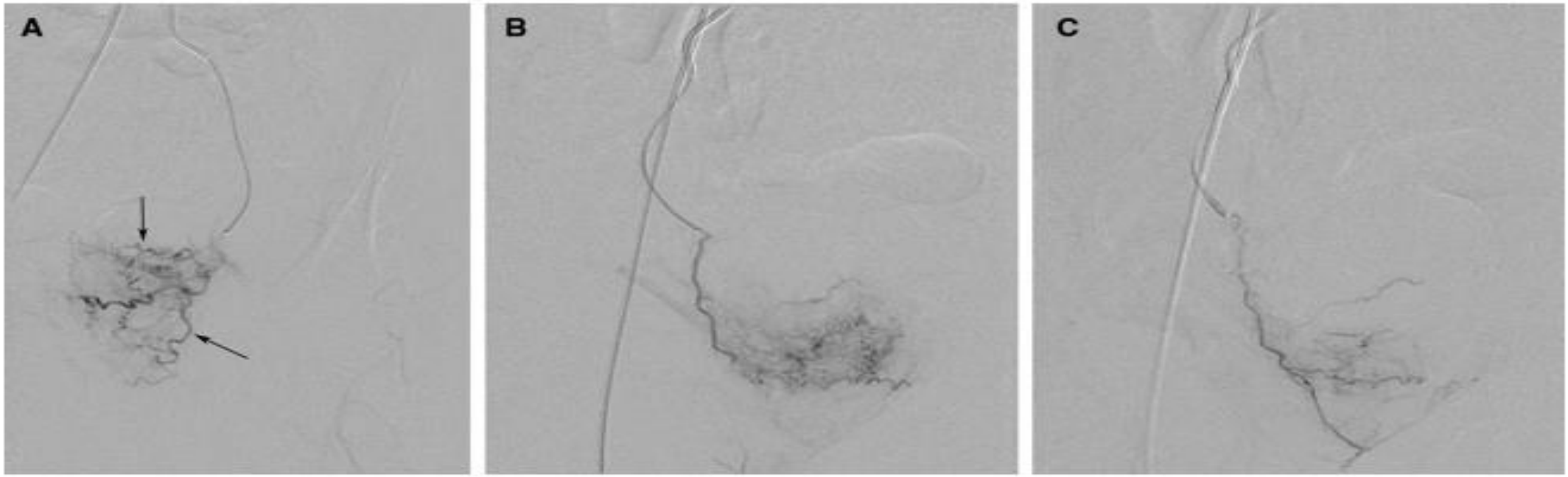
Intravesical application of PRP in patients with persistent HC after HSCT.
A single-center preliminary experience.
Lorenzo Masieri1 . (2019) .Italy

- **10 Patients; BK virus- HC ,post Allo HSCT , 2013 – 2017**
- **Grade 3 or 4 & Refractory to- conservative therapy of HC, Mean P- age 33.6 Y**
- **Transurethral Cystoscopy & PRP, treatment under general anaesthesia**
- **No intra operative complications**
- **Median time to catheter removal ; 6 days**
- **Median length of hospitalization : 35 days**
- **After 30 days :6 p – CR & 3p – PR**
- **Suggestion; intra vesical administration of PRP should be considered**

A Microcatheter angiogram of the left vesical arteries shows enlarged branches and capillary staining (arrows). B There is a similar appearance on the right.
C Following bilateral supraselective embolization.the pathological vascularisation is reduced

A. Garcí a-Gá mez et al: Vesical Artery Embolization in HC.Cardiovasc Intervent Radiol (2016) 39:1066–1069



Hyperbaric oxygen therapy (HBOT)
promotes angiogenesis and tissue healing

Retrospective studies on the effectiveness of HBOT in the treatment of HC after HSCT - hemorrhagic cystitis

HBOT - hyperbaric oxygen therapy, ATA - atmosphere absolute pressure, CR - complete response, NA - data not available.Scientific Reports | (2024) 14:24658

Reference	Inclusion criteria	Sample	HBOT treatment profile	HBOT sessions	Response rate	Adverse effects rate
Cesaro S et al. (2003)[7]	HC after HSCT in paediatric patients	14	2.5 ATA, 110'	Median 17 [4–38] days	CR 78.5%	0%
Yenerel MN et al. (2009)[8]	HC after allogeneic HSCT	7	2.5 ATA, 120'	Median 40 [35–60] sessions in patients with CR	57.1%	14.3%
Savva-Bordalo et al. (2012)[2]	BK-virus-associated HC after allogeneic HSCT	16	2.1 ATA, 90'	Median 13 [4–84] sessions in patients with CR	CR 94.0%	25.0%
Zama D et al. (2013)[9]	Late-onset HC after HSCT in pediatric patients	10	2.2 ATA, 107'	Median 10 [8–30] sessions	CR 70%	NA
Costa D et al. (2015)[21]	Late-onset HC after HSCT	17	2.5 ATA, 90'	Median 20 [4–51] sessions	CR 82%	NA

JoanaArana Ribeiro1. Scientific Reports | (2024) 14:24658

HBOT carries some risks.

Good tolerance even in the pediatric .

HBOT Risks : 30.1% for HBOT,Higher incidence in patients who underwent more than 10 sessions & a therapeutic profile with a chamber pressure above 2.0 ATA:

- ❑Risk of central nervous system oxygen toxicity ;Seizure (less than 0.03% , in an analysis of 20-y & over 180,000 HBOT sessions…)
- ❑Pressure intolerance
- ❑Middle ear barotrauma
- ❑Confinement anxiety
- ❑Intolerance to the helmet
- ❑Abdominal pain

Turkey(2022) ;HBOT .the years 2000–2020 for HC &HSCT

- 25 p ;a median of 12 HBOT sessions .Complete healing 11 p/25 & haematuria improved in 7 p.7 or more HBOT sessions,benefit the most

- **Toxic effects of oxygen and recommended avoiding HBOT in HC patients with Fanconi anemia.**
- **The only patient who remained unresponsive to HBOT in another study also had Fanconi anaemia which the author presented as a relative contraindication**

Diving and Hyperbaric Medicine Volume 52 No. 1 March 2022 27

Hyperbaric oxygen treatment for refractory haemorrhagic cystitis occurring after chemotherapy and haematopoietic stem cell transplantation: retrospective analysis of 25 patients

Handan Ozturk[1], Bengusu Mirasoglu[2], Samil Aktas[2]

[1] Ankara Numune Research and Training Hospital, Underwater and Hyperbaric Medicine Department, Ankara, Turkey
[2] Istanbul University, Istanbul Faculty of Medicine, Underwater and Hyperbaric Medicine Department, Istanbul, Turkey

Cell Therapy ;MAnagement of BKv HCHC Virus-specific T-cell therapy to treat BK polyomavirus infection in bone marrow and solid organ transplant recipients. Adam S. NelsonCell Therapy . Blood advances.2020

❑Mesenchymal Cells

❑Cellular Immune Therapy (Virus-specific T-cell therapy):

- Clearance of BKPyV was associated with recovery of BKPyV-specific T cells in the host.
- Prophylactic infusion of VSTs targeting BKPyV???? **2 weeks after HSCT**

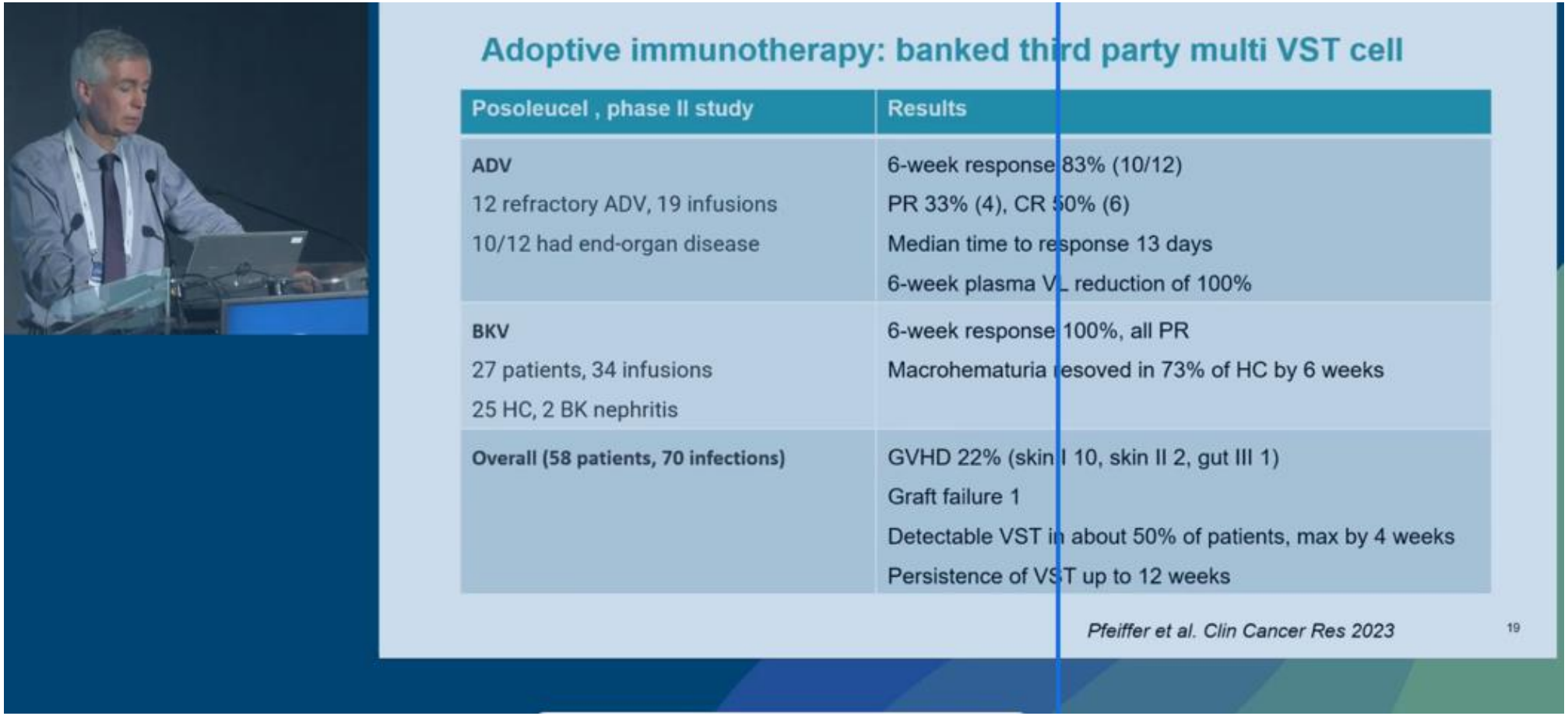
Virus-specific T-cell therapy to treat BK polyomavirus infection in bone marrow and solid organ transplant recipients

Adam S Nelson.Blood Adv .2020. Cincinnati Children's Hospital, Cincinnati, OH.

VSTs;treat BKP yV in 38 HSCTp - & 3SOT p ;**2017 -2019**

- **OR rate 86% -BK viremia & 100% ; in HC**
- No infusional toxicity, de novo GVHD , or rejection of the organ
- KPyV-specific immune responses were demonstrated by interferon-γ production by PB MNC post infusion in response to BKPyV antigens

Adoptive immune therpay Banked third party multi VSt cell. Simone Cezaro. EBMT EBMT 2025



Direct antiviral drug Therapy : NPP-669 preclinicalPhase:Simone Cezaro. EBMT 2025

Direct antiviral drug therapy (V)

NPP-669

- **Prodrug of CDV** containing a long sulfonyl alkyl sidechain (improved lipophylicity)
- Broad-range activity against dsDNA viruses in vitro (ADV, HSV, HVZ, Polyoma, CMV)
- *In Syrian hamster models*:
- Oral NPP-669, dose 1-3 mg/kg, is active against ADV more than BCV
- IV. NPP-669, dose 0.03-0.1 mg/kg, 10 fold more active than oral route
- Reduced gut toxicity and no renal toxicity
- Excellent metabolic and pharmacokinetic parameters,

Tollefson et al Antimicrob Ag Chemother 2024
Lipka et al. Mol Pharmaceutics 2023

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Conclusion

- Bk virus infection represent one of the significant infectious burden for HSCT patients
- There is an **important limit** in the medical intervention for Bk- virsu infections
- **Current Direct Antiviral therapy often is unsatisfying**
- **Adoptive immunotherapy is not accessable to all centers and this is a limit**
- **HBo2 & Bladder Vessels Embolization are used in the management of BKPy V infection in children**

Thank you