European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

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Paula Mazorra & Tobias Feuchtinger

# Disseminated adenovirus disease after HSCT, the role of Cytotoxic T lymphocyte therapy

Moderation: Martin Schalling

Funded by the European Union's EU4Health Programme

SJD Sant Joan de Déu Barcelona · Hospital
Pediatric Cancer Center

SIOPE YOUNG

St. Anna Kinderkrebs Forschung

# COI declaration

- Paula Mazorra: Nothing to declare
- Tobias Feuchtinger: Miltenyi Biotec

# Clinical case

16-year-old female patient

**B Acute Lymphoblastic Leukemia (B-ALL)**

First complete remission after CAR-T Therapy

**CAR-T Therapy**

- **Bridge chemotherapy :** MTX 5 g/m2, DXM, ASP, TIT.
- **High-tumor burden (88%)** before lymphodepletion chemotherapy
- **Complications: CRS g3**
- **Evaluation:** morphologic remission Day +28. CNS negative.

**Haplo-SCT from her mother**

Conditioning: Total body irradiation + Fludarabine

Source: Peripheral blood

GvHD prophylaxis: PT-Cy, Tacrolimus and MMF.

**GI GVHD (s1) and skin GVHD (s2):**

**GVHD global II** → start of Prednisolone 2 mg/kg/day

D 0 | D +29 | D +33 | D +65 | D +73

16 year-old patient

**B-ALL in f**irst complete remission after CAR-T.

**Progenitor infusion**

**AdV reactivation PB**

**Haplo-SCT from her mother**

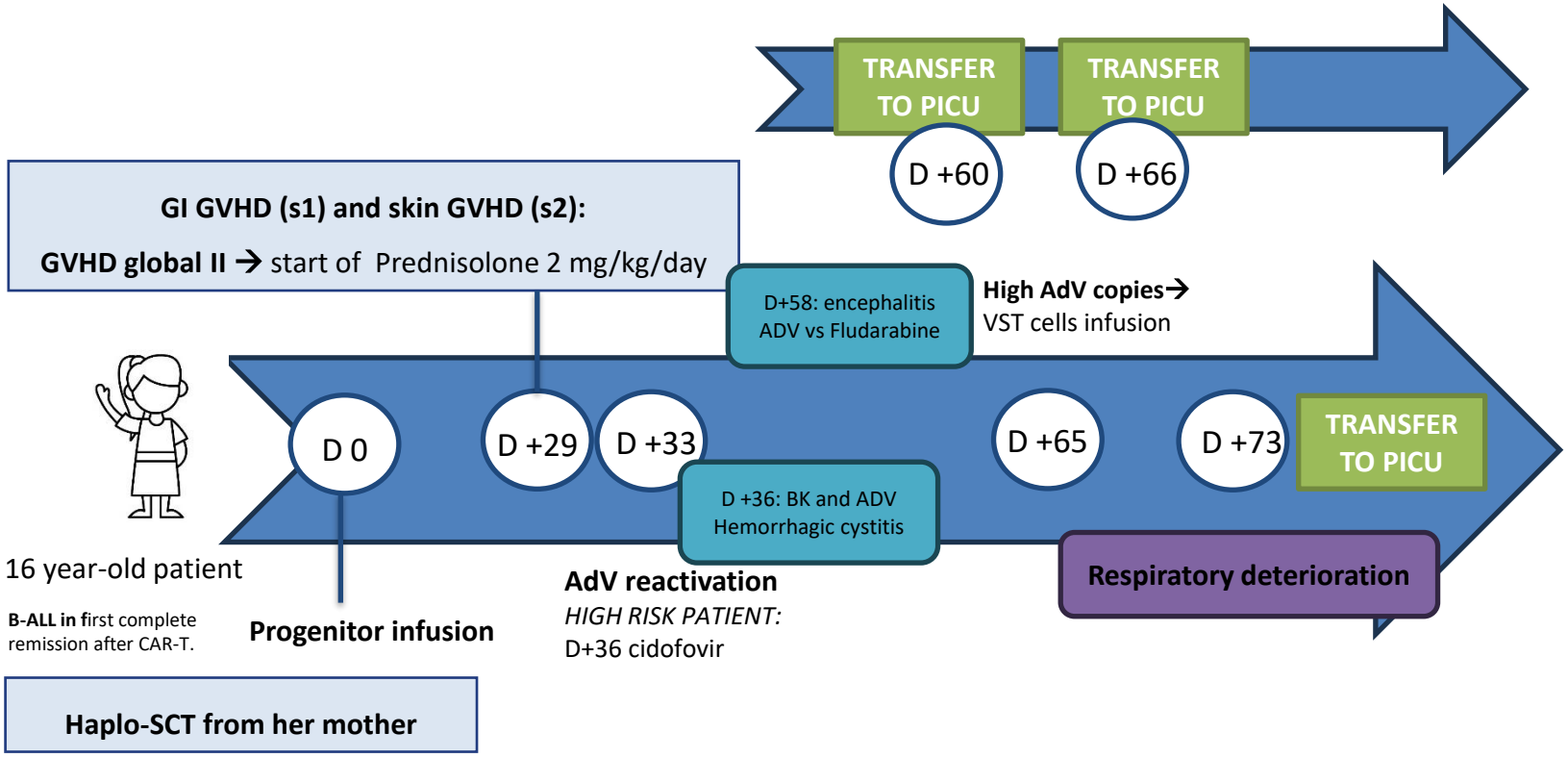
# Question 1

What antiviral would you start as preemptive treatment for Adenovirus reactivation?

1. Cidofovir
2. Aciclovir
3. Ganciclovir
4. Maribavir

# Background

- **Adenovirus infection** after SCT can result in a life-threatening disseminated disease.
- Definitive cure requires adequate immune reconstitution → **cidofovir** to bridge the severely immunocompromised period.
- If cidofovir is not enough, **virus specific T (VST) cell therapy** could be a therapy with promising results.


TRANSFER TO PICU
TRANSFER TO PICU
D +60
D +66
GI GVHD (s1) and skin GVHD (s2):
GVHD global II → start of Prednisolone 2 mg/kg/day
D+58: encephalitis ADV vs Fludarabine
High AdV copies→
VST cells infusion
D 0
D +29
D +33
D +65
D +73
TRANSFER TO PICU
D +36: BK and ADV Hemorrhagic cystitis
Respiratory deterioration
16 year-old patient
B-ALL in first complete remission after CAR-T.
Progenitor infusion
AdV reactivation
HIGH RISK PATIENT:
D+36 cidofovir
Haplo-SCT from her mother

# Question 2

Would you intubate this patient?

1. Yes, we have more therapeutic options
2. Yes, we need to give time to VST cells effect
3. No, she is only candidate to non-invasive ventilation
4. No, she is not a candidate for aggressive measures

# Engraftment

16 year-old patient

**B-ALL in first complete remission after CAR-T.**

**Haplo-SCT from her mother**

NEUTROPHIL D+23
PLATELET D+26

D 0

D +29

D +33

**AdV reactivation**
D+36 cidofovir

D+58: encephalitis

D +36: Hemorrhagic cystitis

D +65

**High AdV copies→** VST-cells infusion

D +73

**TRANSFER TO PICU**

**Respiratory deterioration**

# GVHD

16 year-old patient

**B-ALL in first complete remission after CAR-T.**

**Haplo-SCT from her mother**

**GVHD global II →** Prednisolone 2 mg/kg/day

**1st ENDOSCOPY (D+30) :** GVHD G3

**STOP MMF**

**2nd ENDOSCOPY (D+71):** GVHD vs AdV

**High AdV copies→**
VST cells infusion

D 0 | D +29 | D +33 | D+58: encephalitis | D +65 | D +73 | **TRANSFER TO PICU**

D +36: Hemorrhagic cystitis

**AdV reactivation**
D+36 cidofovir

**Respiratory deterioration**

**STOP PREDNISOLONE (D+64)**

**GVHD GI IV→** Ruxolitinib 5 mg/12h (D+67)

**MESENCHYMAL CELLS**

# AdV copies and lymphocyte subpopulations

16 year-old patient

**B-ALL in first complete remission after CAR-T.**

**Haplo-HSCT from her mother**

D 0

D +29

D +33

D+58: encephalitis

1.740.111 cp/mL

CNS +

D +36: Hemorrhagic cystitis

**High AdV copies→**
VST cells infusion

5.486.019 cp/mL

D +73

TRANSFER TO PICU

**GVHD global II**

47 cp/mL

**AdV reactivation**
D+36 cidofovir

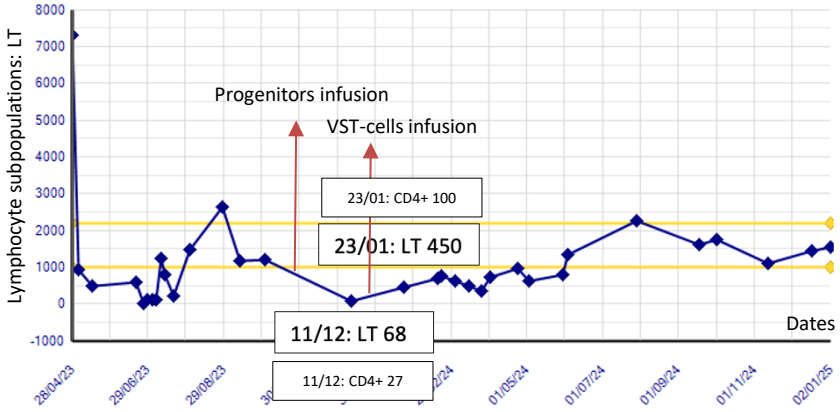
324-833 cp/mL

**Respiratory deterioration**

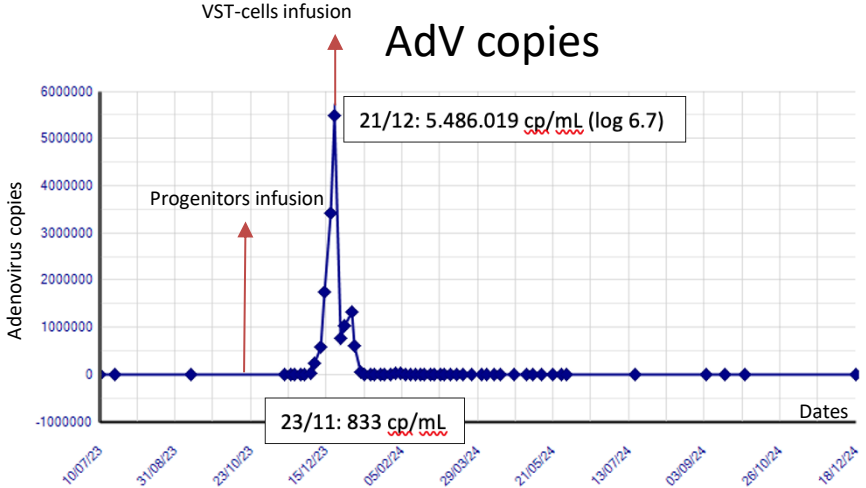
1.017.665 cp/mL

ELISPOT positive D+14

## Lymphocyte subpopulations




## AdV copies



# Adenovirus reactivation

Blood. 2010 Dec 16; 116(25): 5476–5485.
Prepublished online 2010 Sep 13. doi: 10.1182/blood-2010-04-259291
PMCID: PMC3031399
PMID: 20837781
*How I treat*

**How I treat adenovirus in hematopoietic stem cell transplant recipients**

Caroline A. Lindemans,[1] Ann M. Leen,[2] and Jaap Jan Boelens[1]



## 1. Antiviral drugs

- Preemptive treatment
- Cidofovir 5 mg/kg weekly or 1 mg/kg 3 times a week
- Clearence only occures when T cells reconstitute after SCT

## 2. Donor lymphocyte infusions (DLIs): significant toxicity

## 3. ADV-specific cytotoxic T cells

- Reconstitution of the immune system
- Effect: **10-15 days**

# Adenovirus reactivation

**HIGH RISK:**

- CB donor/T cell depleted graft recipient < 1mo post-SCT
  - AND/OR
- Immuno-supression
  - Prednisone > or = 1 mg/kg/day and > o = 1 Lympho. Prolif Inh

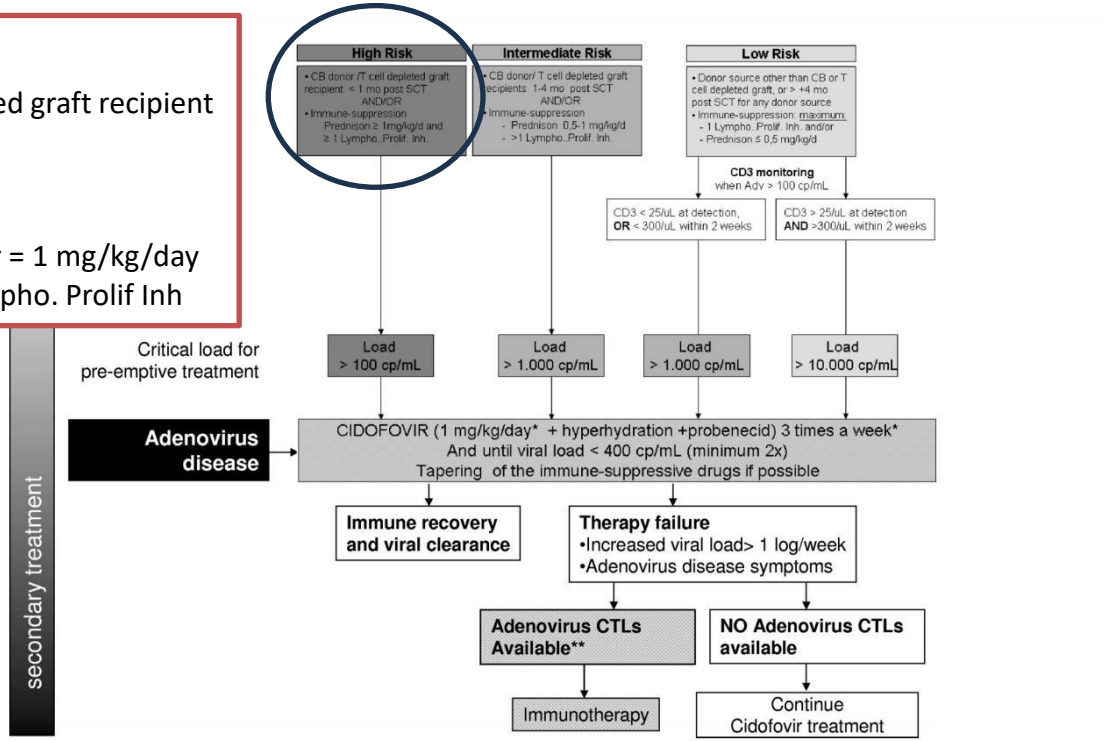



**Figure 2. How I treat AdV in HSCT recipients: treatment guideline.** Refer to the text for a detailed explanation. Lympho. Prolif. Inh. Indicates lymphocyte proliferation inhibitor (eg, cyclosporin A, CsA); *alternative cidofovir 5 mg/kg intravenously weekly. **For centers that have the AdV CTLs readily available, CTLs are immediately initiated for all high-risk patients and for all patients with AdV symptoms before awaiting cidofovir effect.

# Adenovirus reactivation

- **Systemic infection/viremia:** Positive PCR, virus isolation or Ag detection in blood

- **Probable disease:** Infections plus symptoms and signs without histological confirmation
  - Detection AdV in stool + enteritis
  - Detection of AdV in urine + nephritis
  - Detection of AdV in PB+: fever, enteritis, hepathopathy, nephritis

- **Proven disease:** Infection plus symptoms related to the infection and histological confirmation
  - Detection of AdV in organ biopsy
  - Detection of AdV in cerebrospinal fluid
  - Multiple organ failure, high viral load in PB and detection of AdV in autoppsy

# Adenovirus reactivation

## ECIL- Management of adenovirus infections

## High risk patients

- In-vivo or ex-vivo T-cell depletion
- Unrelated donor graft
- Unrelated cord blood graft
- Severe (Gr III-IV) graft versus host disease
- Severe lymphopenia (<300 CD3+ cells/ul PB)

**Prophylactic virostatic treatment:** not recommended

**Preemptive treatment asymptomatic viremia:** viremia **+ at least one risk factor**

**Treatment indication:** proven or probable AdV disease

1. **Antiviral drugs:** Cidofovir
2. **Other options**: Ig, virus specific CTLs, reduction/withdrawal of immunosuppression

# Adenovirus reactivation

**Virus-specific T cells for adenovirus infection after stem cell transplantation are highly effective and class II HLA restricted**

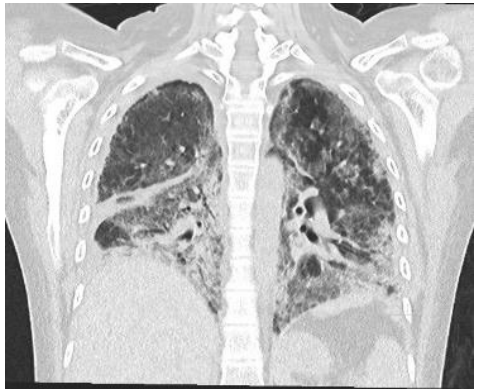
Clinical Trials & Observations

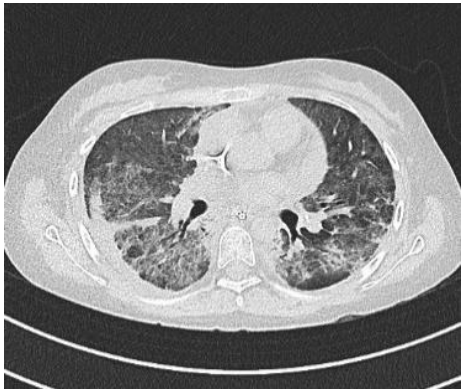
Jeremy D. Rubinstein, Xiang Zhu, Thomas Leemhuis, Giang Pham, Lorraine Ray, Sana Emberesh, Sonata Jodele, Shawn Thomas, Jose A. Cancelas, Catherine M. Bollard, Patrick J. Hanley, Michael D. Keller, Olivia Grimley, Diana Clark, Teri Clark, Cecilia S. Lindestam Arlehamn, Alessandro Sette, Stella M. Davies, Adam S. Nelson, Michael S. Grimley, Carolyn Lutzko

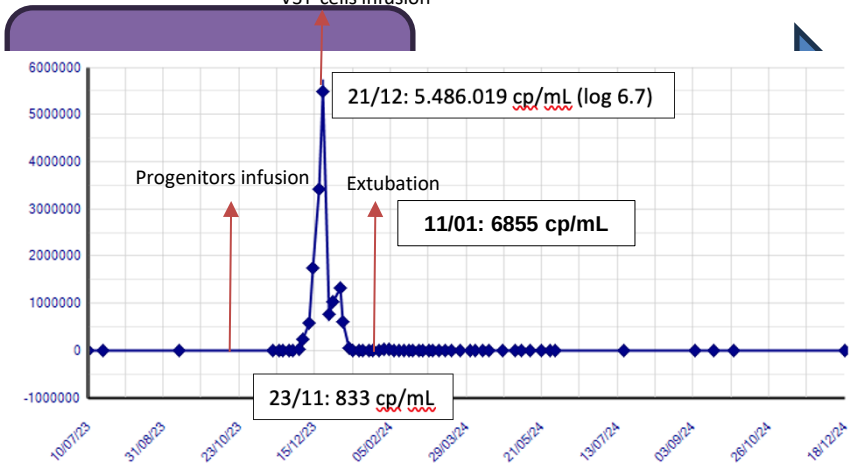
Check for updates

*Blood Adv* (2021) 5 (17): 3309–3321.

- **30 patients** with 43 infusions: 7 patients donor-derived VST, 21 patients third-party, 2 both.
- Response was evaluated 4 weeks after the infusion.
- Median time adenovirus reactivation: day +28. Median viral load: 43.323 copies/ml.
- 3 patients died within 10 days of infusion, 1 transitioned to hospice → no evaluable.
- **Clinical response: 81%,** complete response 58%.
- Safety: No severe infusion reactions, GVHD 2.6% cases.
- 5 patients who never achieved a response: 4 third-party and 1 third-party + donor–derived.
  - ¾ received >1 infusion → no response.








D +85

**EXTUBATION**
20d after VSTs inf

**HOME DISCHARGE**

*No respiratory support*

***Alive and well after 1,5 years post-trasplant***

*3 weeks after the VSTs therapy was performed…* **She started to improve**

# Question 3

What is your main diagnostic suspicion?

1. Adenovirus reactivation — Adenovirus copies decreasing
2. Pulmonary fibrosis — CT resolved after treatment
3. New infection — No microbiological findings
4. VST-cells pulmonary involvement — No data available, no biopsy
5. Transfusion-related acute-lung injury — No temporally related
6. Ventilator-associated lung injury — No temporally related

?

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# DISCUSSION

Funded by the European Union's Health Programme

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# Take home messages

- Disseminated adenovirus disease negatively affects transplant outcomes and can be a fatal complication.
- Traditional antiviral therapies (cidofovir) have **limited efficacy** and significant side effects, particularly nephrotoxicity.
- The **role of VST-cells** aims to restore the immunity and treat established infections. Limited pediatric experience.
- 3-4 weeks should be waited to see the effects of the VST-cells therapy, being decisive in the decisions taken.
- New therapies, new adverse effects→ **new challenges.**

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# ¡Thank you!

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# References


- Lindemans C, Leen A, Boelens J. How I treat adenovirus in hematopoietic stem cell transplant recipients. Blood, 2010 Dec 16; 116(25): 5476-5485.
- Rubinstein J, Zhu X, Leemhuis T et al. Virus-specific T cells for adenovirus infection after stem cell transplantation are highly effective and class II HLA restricted. Blood Adv, 2021; 5(17): 3309-3321.
- Annaloro C, Serpenti F, Saporti G et al. Viral infections in HSCT: Detection, monitoring, clinical management and immunologic implications. Front- Immunol, 2021; 11:569381.
- Matthes-Martin S, Feuchtinger T, Shaw P, Engelhard D and Ljungman P. Management of adenovirus (ADV) infections 4th European Conferene of Infections in Leukaemia. September 8-11th, 2011.