Neurological Complications after allogeneic HSCT

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Neurological Diagnostic Challenges after HSCT

- Malignancies
- Psychiatric manifestations
- Intracerebral hemorrhage
- PRES
- IST neurotoxicity
- Ischemic stroke
- Seizures
- Infections
- GvHD
- Neuromuscular complications
The growth of allogeneic transplantation as a therapeutic modality in the past 5 decades, and the increased survival in many transplant recipients, has been associated with the emergence of new patterns of disease including a range of acquired neurological disorders some of which had never been characterized in the pre-transplant era.

Transplant-associated neurological complications involve the central and/or peripheral nervous systems may occur in the acute posttransplant setting or months to years later.

It is estimated that one third of transplant recipients experiences clinically significant neurological alterations: incidences ranging from 11% to 70% depending on the populations studied and the types of neurological diseases identified.

Autopsy studies suggest that an even higher proportion of transplanted patients have neurological injury which may not be clinically recognized.

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### Integrated Diagnostic Approach

| Laboratory evaluation | • blood count, schistocytes, LAD  
| | • liver and kidney function tests, electrolytes  
| | • immunosuppressive serum drug levels  
| | • serological and microbiological tests for known pathogens |
| CSF analysis | • PCR assays for viral pathogens  
| | • exclusion of malignancies |
| Imaging | • CT scan  
| | • MRI of brain and spinal cord |
| Electrophysiologic testing | • electroencephalogram (EEG)  
| | • electromyogram (EMG)  
| | • nerve conduction studies (NCS) |
Neurological Diagnostic Challenges after HSCT

Neurotoxicity is common with calcineurin inhibitors (CNIs): occurs more commonly with tacrolimus (21%) than CsA (12%).

Reported clinical manifestations: fine tremor responsive to β-blockade, neuralgia, and peripheral neuropathy. More severe presentations affect 5% to 10% of patients: psychosis, cortical blindness, seizures, cerebellar ataxia, motor weakness, obtundation, and coma.

Drug-Related Neurotoxicity

**Neurotoxicity of Immunosuppressive Agents**

- Immunophilin Ligands (CNIs)
- Corticosteroids
- OKT3 and Other Monoclonal Antibody (alemtuzumab, rituximab)
- Vincristine, cisplatin, ifosfamide, MTX
- RT
- Cytarabine
- Busulfan
- L-asparaginase
- Steroids

**Clinical manifestations:**

- Leukoencephalopathy
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Peripheral Neuropathy
Steroid-Related Neurotoxicity

Atrofia cerebrale
non correla il grado di funzione neuropsicologica di questi pazienti

Citarabine-Related Encephalopathy

- Sindrome cerebellare ± disfunzioni cerebral reversibili: compare 6-8 gg dalla somm, è dose dipendente (> 54 g/m²)
  
  Lazarus HM, Cancer. 1981

- Reversible posterior leukoencephalopathy syndrome (PRES): dose indipendente

- Mielopatia: ARA-C it /ev
  
  Dunton SF et al Cancer

Bungo Saito, American Journal of Hematology (2007)
MTX-Related Leucoencephalopathy

“On MRI, methotrexate leucoencephalopathy is basically similar to RT leucoencephalopathy”

- Risparmio della S.G. e delle fibre “u” sub-corticali
- Demielinizzazione focale o diffusa
- Aree di necrosi della SB (soprattutto posteriormente ai ventricoli)
- Microangiopatia mineralizzante
- Calcificazioni
- Danno della glia

Busulfan-Related Neurotoxicity

- Frequenza: 10% (adulti), 7.5% (bambini)
- Dose dipendente (alte dosi 600mg/m2)
- Clinica: Convulsioni tonico-cloniche/miocloneiche (spesso dopo le ultime dosi: prolungata esposizione al Busulfano e/o ai suoi metaboliti)

- Profilassi anticonvulsiva (Eberly AL Pharmacotherapy, 2008):
  1° scelta Clonazepam (anche i.c),lorazepam
  2° scelta fenintoina (tox epatica) carbamazepina

  Iniziare 2-3 gg prima del Bus e scalare dopo 72-96 ore dopo ultima dose

(Meloni G, Haematologica, 1995)
L-Asparaginase Neurotoxicity

Diatesi emorragica + Diatesi trombotica:
- Infarti corticali (spesso multipli)
- Trombosi dei seni
- Emorragie cerebrali (rare)
- PRES (Rathi B Pediatr Neurosurg. 2002)
- Neurotossicità compare rapidamente (entro 1° gg)

Peripheral Neuropathy

Neuropatie Sensoriali e/o Motorie:
Dose cumulativa e durata dipendenti

<table>
<thead>
<tr>
<th>Farmaco</th>
<th>% Onset</th>
<th>Sensorio %</th>
<th>Motorio %</th>
<th>Out come</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcaloidi della Vinca</td>
<td>75%*</td>
<td>30-40%</td>
<td>5-10%</td>
<td>100% risolve &gt; 4 mesi</td>
</tr>
<tr>
<td>(VCR, Vindesina, Vinblastina, Vinorelbide)</td>
<td>2 sett</td>
<td>Distale simm. (parestesie,ileo paralitico ecc..)</td>
<td>Muscoli estensori mani/piedi e dorsi-llessori dei piedi Debolezza muscolare simmetrica,disartria, disfagia ecc..</td>
<td></td>
</tr>
<tr>
<td>Composti contenenti Platino: Cisplatino</td>
<td>10-40%</td>
<td>Distale simm. (+/- dolorosa)</td>
<td>Normale</td>
<td>20-60% risolve &gt;molti mesi</td>
</tr>
<tr>
<td>(dose cumulativa &gt; 300 mg/m² S.C.), Carbo,Oxaplatino</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talidomide</td>
<td>20-40%</td>
<td>20-40%</td>
<td>Rara debolezza muscolare</td>
<td></td>
</tr>
</tbody>
</table>

J. of Peripheral Nervous System, 2008
Late Effects of Childhood Cancer. chapter 2a
Posterior Reversible Encephalopathy Syndrome (PRES)

Clinical–radiographic syndrome of headache, visual disturbances (cortical blindness), confusion, seizures, or coma.

- A pattern of vasogenic edema involving the parietal and occipital white matter—with abnormalities resolving within weeks following treatment or correction of the precipitating circumstance.

- Common precipitating factors are acute hypertension, immunosuppressive and chemotherapeutic agents, eclampsia, infection, and autoimmune diseases.

- The incidence of PRES after allogeneic HSCT using MAC preconditioning and cyclosporine or tacrolimus is 3% to 16%, depending on the aggressiveness of the preconditioning and TBI.

- Management of PRES is centered on
  (a) identifying and treating the underlying precipitating factor (discontinuing CNI therapy) and (b) treating brain edema and seizures.

  Reversibility of symptoms and brain lesions, however irreversible damage may occur in selected patients in whom PRES is complicated by cerebral infarction, or hemorrhage.

Posterior Reversible Encephalopathy Syndrome (PRES)

Farmaci responsabili di PRES

<table>
<thead>
<tr>
<th>Età pediatrica</th>
<th>Età adulta</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA</td>
<td>CsA,Tacrolimus</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>Bevacizumab, Thalidomide,Rituximab</td>
</tr>
<tr>
<td>L-asparaginase</td>
<td>Quasi tutti i CT: Gemcitabine,Doxorubicin,CY,VCR,</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Cisplatinum,5-Flourouracil,MTX,ARA-C,</td>
</tr>
<tr>
<td>ATRA</td>
<td>Carboplatin, Bleomycin,VP16,irinotecan,</td>
</tr>
<tr>
<td></td>
<td>Oxaliplatin,Paclitaxel,Vinblastine</td>
</tr>
</tbody>
</table>

Neurotossicità da CsA

Second to renal toxicity, neurotoxicity is the most serious side effect with cyclosporine affecting 25% to 59% of transplant patients

Biochemical mechanisms of cyclosporine neurotoxicity
**Posterior Reversible Encephalopathy Syndrome (PRES)**

**Fattori scatenanti la PRES da CNIs:**

- **Toxicità diretta** (anche se i livelli sono spesso nei range):
  - Alterazione della barriera emato-encefalica
  - Rilascio di vasocostrittori (endotelina-tromboxano)
  - Anomalo metabolismo della CSA (disfunzioni epatiche)
  - Ipocolesterolemia

**Danno endoteliale:**
- Microangiopatia trombotica (TTP)
- GvHD acuta severa (>2 grado)
- Ipertensione arteriosa

**Altro:**
- Ipomagnesemia
- Reazioni anafilattiche, infezioni
- Alcune terapie concomitanti

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**Posterior Reversible Encephalopathy Syndrome (PRES)**

**Patogenesi della PRES**

- Danno endoteliale: rilascio di endotelina, prostacicline e tromboxane A
- "Cytokine storm": ipertensione arteriosa
- Autoregolazione-Vasocostrizione
- L’innervazione simpatica è più rara nella circolazione posteriore
- "Breakdown" dei meccanismi autoregolatori
- Vasodilatazione
- Aumento della pressione capillare idrostatica
- Fuoriuscita di fluidi
- Edema vasogenico

Due opposte teorie:
1. La grave ipertensione supera i meccanismi autoregolatori cerebrali: edema cerebrale
2. L’ipertensione induce una autoregolazione del flusso cerebrale con vasocostrizione, ischemia e conseguente edema cerebrale
Posterior Reversible Encephalopathy Syndrome (PRES)

MRI:
T2 and FLAIR hyperintensity, prevalently subcortical, occipito-parietal.

Neurological Diagnostic Challenges after HSCT

<table>
<thead>
<tr>
<th>Ischemic stroke</th>
<th>Malignancies</th>
<th>Infections</th>
<th>PRES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>Intracerebral hemorrhage</td>
<td>IST neurotoxicity</td>
<td>Neuromuscular complications</td>
</tr>
<tr>
<td>GvHD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Psychiatric manifestations

- Anxiety disorders, mood disorders, and suicide
- Posttraumatic stress disorder, depression, mania, and psychosis
- Corticosteroids may have very prominent behavioral effects
- Influence of the life-threatening nature of the patients' medical conditions
Neurological abnormalities in TA-TMA

Neurological symptoms in TA-TMA are typically transient and fluctuating.

At diagnosis of TA-TMA up to 60% of patients can present neurological abnormalities, 90% during the course of disease.

Neurological clinical manifestations:
- Altered mental status (confusion, disorientation)
- Focal neurological signs
- Headache
- TIA, aphasia, dysarthria
- Paresthesia, Paresis, Paralysis
- Consciousness loss
- Ataxia, dizziness
- Visual alterations

Transplantation-associated thrombotic microangiopathy (TA-TMA)

- TA-TMA, a significant complication of HSCT.
- Family of thrombotic microangiopathies (HUS, TTP).
- TA-TMA occurs when endothelial injury in the context of HSCT causes microangiopathic hemolytic anemia and platelet consumption, resulting in thrombosis and fibrin deposition in the microcirculation.
- The kidney is most commonly affected, but neurological injury has been reported.
- Mortality rates often high.
- Close association with other post-HSCT complications such as GVHD and infections.
Vascular injuries to the endothelium post SCT

Initiating events, such as CT and RT may lead directly to endothelial damage and/or dysfunction. A procoagulant phenotype expressed by injured endothelial cells promotes activation and adhesion of platelets.

Further events during the course of transplantation, such as the development of GVHD, administration of CsA and possibly infection, may lead to further endothelial cell dysfunction or apoptosis mediated directly or through the elaboration of proinflammatory cytokines.

**Classical diagnostic pentad (40%) of TA-TMA:**
- Microangiopathic hemolytic anemia
- Thrombocytopenia
- Renal failure
- Fever
- Neurological abnormalities

**Classification and Prognosis of TA-TMA**

<table>
<thead>
<tr>
<th>Diagnostic criteria for TA-TMA.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated above the upper limit of normal for age.</td>
<td>Elevation in lactate dehydrogenase (LDH).</td>
</tr>
<tr>
<td>Hypertension.</td>
<td>A random urine protein concentration of &gt; 30 mg/dL.</td>
</tr>
<tr>
<td>De novo thrombocytopenia</td>
<td>A blood pressure at the 95th percentile value for age, sex, and height.</td>
</tr>
<tr>
<td>De novo anemia</td>
<td>Thrombocytopenia with a platelet count &lt; 50 × 10^9/L.</td>
</tr>
<tr>
<td>Elevated plasma concentration of C3b-9 h</td>
<td>A hemoglobin below the lower limit of normal for age or anemia requiring transfusion support.</td>
</tr>
<tr>
<td>Elevated plasma concentration of C3b-9 h</td>
<td>Elevated plasma concentration of C5b-9 h above upper normal laboratory limit.</td>
</tr>
</tbody>
</table>
Brain MRI: Hyperintense FLAIR signal involving the bilateral (left and right) cortex and subcortical white matter. Effacement of sulci suggests associated swelling. Findings are suggestive of PRES.

Although neurologic deficits have been reported in up to half of all patients with TA-TMA, a detailed understanding of central nervous system (CNS) disease remains elusive. Manifestations can include confusion, headaches, hallucinations, or seizures.

Although the CNS vasculature can certainly be affected by TA-TMA, the most common TA-TMA-related CNS injury is likely due to acute uncontrolled TMA-associated hypertension, including PRES that may result in CNS bleeding. PRES may present with headaches, visual disturbances, mental status changes, or seizures.

Neuroimaging reveals signal abnormalities in posterior portions of the brain but can include the brainstem, cerebellum and basal ganglia, and symptoms are often preceded by significant hypertension.

#### Neurological manifestations in hemolytic–uremic syndrome

Weissenborn, Neuroradiology (2013).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/gender</th>
<th>Time between disease onset and MRI (days)</th>
<th>Neurological findings at time of MRI examination</th>
<th>Neurological findings at time of discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>25/f</td>
<td>9</td>
<td>Disorientation for time, deficit in working memory and recall; MMS: 15</td>
<td>No neurological deficit</td>
</tr>
<tr>
<td>B</td>
<td>24/f</td>
<td>16</td>
<td>Bouts of unilateral synoptosis, blurred vision, trouble finding words; hyporeflexia, intention tremor, dysmetria; MMS: 10</td>
<td>No neurological deficit</td>
</tr>
<tr>
<td>C1</td>
<td>27/f</td>
<td>8</td>
<td>Trouble finding words, deficit in working memory, headaches; MMS: 27</td>
<td>No neurological deficit</td>
</tr>
<tr>
<td>C2</td>
<td>27/f</td>
<td>10</td>
<td>Trouble finding words, slight deficit in working memory, bouts of double vision, psychomotor slowing, headaches; MMS: 29</td>
<td>No neurological deficit</td>
</tr>
<tr>
<td>D</td>
<td>41/f</td>
<td>13</td>
<td>Trouble finding words, bouts of double vision, slight depression; MMS: 29</td>
<td>No neurological deficit</td>
</tr>
<tr>
<td>E</td>
<td>46/f</td>
<td>11</td>
<td>Super MMS: 0</td>
<td>Slight ataxia, hyporeflexia, double-finding words</td>
</tr>
<tr>
<td>F1</td>
<td>50/f</td>
<td>10</td>
<td>Patient is sedated and mechanically ventilated because of the use of adverse effects of drugs</td>
<td>Persistent nightmares, asthenic gait</td>
</tr>
<tr>
<td>F2</td>
<td>50/f</td>
<td>26</td>
<td>Dizziness, mental delusions, and psychomotor disturbances</td>
<td>Persistent nightmares, asthenic gait</td>
</tr>
<tr>
<td>G</td>
<td>55/f</td>
<td>23</td>
<td>Disorientation, dysarthria, tinnitus; MMS: 23</td>
<td>Slight cognitive deficits, mild tinnitus</td>
</tr>
<tr>
<td>H</td>
<td>55/f</td>
<td>27</td>
<td>Patient is sedated and mechanically ventilated, shows recurrent focal seizures despite of barbiturate treatment</td>
<td>Mild tinnitus, dysesthesia</td>
</tr>
<tr>
<td>I</td>
<td>57/f</td>
<td>12</td>
<td>Deficit in attention, working memory, memory, apraxia, trouble finding words; MMS: 22</td>
<td>Slight memory and attention deficits, fatigability</td>
</tr>
</tbody>
</table>

*MMS Mini-Mental Status*
A discrepancy often exists between bland or mild cerebral MRI findings and severe neurological symptoms. Hypothesis: the metabolic–toxic changes predominantly affect brain function on a microstructural level instead of a macrostructural level, resulting in inconspicuous conventional MRI findings. Quantitative analysis of routine clinical MRI sequences in the acute phase of STEC–HUS can be more sensitive: prolonged T2 relaxation time indicates cerebral microstructural damages.

Cerebral damage in hemolytic–uremic syndrome

Neurological Diagnostic Challenges after HSCT

<table>
<thead>
<tr>
<th>DIFFERENTIAL DIAGNOSIS OF ENCEPHALITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancies</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>Cerebral vasculitis</td>
</tr>
</tbody>
</table>

Malignancies | Drug-induced | Bacterial, Lyme disease, Neurosyphilis | Parasitic
Sarcoïdosis | Adenovirus, Enterovirus | Fungal | HSV 1-2, HHV6
Cerebral vasculitis | TBC | Toxoplasmosis | VZV, EBV, CMV
Viral infections: Encephalitis

Headache, confusion, memory problems and fatigue.

HHV-6 Acute Limbic Encephalitis: MRI

EEG: sharp waves in both of the temporal lobes, epileptic seizures in right temporal lobe.

CSF analysis: PCR assays for viral pathogens.

Infections such as CMV and HHV-6 have been associated in case reports with TA-TMA.

Human-herpes-virus-6-related acute encephalitis as a major diagnostic and therapeutic challenge after haploidentical stem cell transplantation
Post-HSCT HHV-6 disease

- Well known in Cord blood transplant\(^1\)

- Demonstrated impact\(^2\) on
  - Engraftment (delayed platelet engraftment)
  - Acute GVHD
  - Overall mortality

- Multi-organ involvement
  - Skin rash
  - Cholitis/diarrhea
  - Mielosuppression
  - Encephalitis

1. Scheurer et al., Bone Marrow Transplantation (2013) 48, 574–580

HHV-6 related encephalitis

- limbic encephalitis + HHV-6 in CS fluid
  (typical clinical and MRI signs)

- even without the evidence of HHV-6 in CSF
  - limbic encephalitis
  - plasmatic high viral load
  - exclusion of other causes of CNS disease
Patients

• 9 years (2009-2017)

• **16 cases** HHV-6 encephalitis after haplo-HSCT
  – M 10, F 6
  – median age 52y
  – PBSC graft
  – 8 AML; 2 ALL; 4 NHL; 2 HD
  – rapamycin-based GvHD prophylaxis
    • 5 anti-thymocyte globulin + rapa
    • 8 PT cyclophosphamide + rapa
  – 3 T-cell depleted graft

Patients

• Baseline prophylaxis:
  13/16 pts receiving acyclovir (10 mg/Kg bid)

• Time of onset:
  25 days after HSCT (median); range 2-218
Clinical presentation

- **acute onset** (all cases)
- **disorientation** (common)
- **confusion** (common)
- **pruritus** (common)
- **memory loss** (4)
- **seizures** (3)
- **hyponatremia** (common; severe in 2 pts)
- **hypothermia** (1)
- **axial myoclonus** (1)

Lab

- **Quantitative PCR**
- **Plasma (reactivation)**
  - all pts
  - median viral load of 15443 copies/µl
    (range 550-101332)
- **Cerebrospinal fluid**
  - LP performed in 9/16 patients
  - HHV-6 positivity in all cases
  - Median viral load 206400 copies/µl
    (range 3187-961350)
MRI

- Limbic encephalitis
  - Insula
  - Hyppocampi
- Gd enhancement
- Negative (5/16)

EEG

- Performed in 14/16 pts
  - Disrupted general organisation (common)
  - Focal slow abnormalities (common)
  - Epileptiform abnormalities (4/14)
Treatment

- All patients received antiviral pharmacological treatment
  - Gancyclovir: 5/16
  - Foscarnet: 5/16
  - Foscarnet + Gancyclovir: 6/16

- Gancyclovir 5 mg/Kg bid
- Foscarnet 90 mg/Kg bid (adj for GFR)
- Descalation strategy

Outcome

Poor (mortality rate: 50%)

- Resolution in 8 cases:
  - 6/8 treated with foscarnet-containing regimen (FSC+GCV or FSC)
  - with sequelae (common): memory loss, mild cognitive impairment

- Immune reconstitution
  - 67% in pts with >100 CD3+/µl
  - 28% in pts with <100 CD3+/µl
Conclusion

• Poor prognosis after haplo-HSCT

• Common antiviral prophylaxis not effective

• Early (combined) antiviral therapy

• Regular plasma HHV6 monitoring? → prospective study

HHV6-specific T-cells to predict HHV-6 infection after allo-HSCT
40-50% of patients undergoing HSCT experience HHV-6 reactivation.

Clinical manifestations:
- Fever
- Skin rash
- Gut involvement
- Pulmonary complications
- Neurological disorders
- Delayed engraftment
- Poor Graft Function.

HHV6 reactivation after HSCT is a predictor for poor clinical outcome

Higher incidence of aGvHD

Higher NRM rates

De Pagter, et al, BMT 2013

2009-2013: we evaluated haematological patients who developed positivity to HHV-6 after allogeneic HSCT (54 pts).

At the moment of HHV6 reactivation all patients were receiving acyclovir as antiviral prophylaxis except 5 (3 off antiviral therapy, 2 on ganciclovir).

Viral DNA was isolated from different specimens (peripheral blood, bone marrow, BAL, gastrointestinal biopsy, cerebrospinal fluid) using a quantitative PCR (Nanogen).

Median time of onset: 34 days

Organ involvement was documented also in patients with negative plasma DNAemia test.
Clinical Manifestations

79% fever
37% skin rash
31% hepatitis
46% diarrhoea

31% cytopenia
21% delayed engraftment
29/54 pts: acute GvHD
(III-IV grade predominance)

10 cases of HHV6 encephalitis

Antiviral therapy
• necessary in 63% cases
• 67% received foscarnet

Outcome
• Mortality rate was relatively high in this population, mainly related to severe infections or GvHD.
• OS ± SE at 1 year after HHV-6 reactivation was 38% ± 7%.

Immunoreconstitution

OS from HHV6 Reactivation

OS (univariate) HR (CI 95%) p-value
CR vs disease 0.26 (0.07-0.89) 0.032
aGvHD 3/4 2.08 (1.08-4.03) 0.029
CD3+ ≥ 200/mcl 0.27 (0.13-0.54) 0.0002

OS was not significantly influenced by steroids administration, time after alloSCT, type of antiviral prophylaxis, plasma viral load and organ involvement.
HHV6+ 131 pts (62%). Median time to HHV6 positivity: 25 days after HSCT. 2nd reactivation and/or organ involvement: 40%. Antiviral treatment (GCV, FSC) in 40% of reactivating patients.

HHV6 Positivity and Clinical Manifestations

Viral load: weekly monitored by quantitative PCR in plasma.

Clinical manifestations:
- hepatitis (19),
- diarrhoea (28),
- encephalitis (5),
- BM suppression (30),
- delayed engraftment (13),
- fever (42),
- skin rash (57).

HHV6+ 62%.

Only 40% of reactivating patients with clinically relevant infection.

Donors were:
- family haploidentical (104),
- HLA identical sibling (39),
- unrelated (63),
- cord blood (7).

Graft source: PBSCs (87%). MAC 84%. GvHD prophylaxis: ATG 40%, PT-Cy 49%.

Donors were:
- family haploidentical (104),
- HLA identical sibling (39),
- unrelated (63),
- cord blood (7).

Graft source: PBSCs (87%). MAC 84%. GvHD prophylaxis: ATG 40%, PT-Cy 49%.

aGvHD: 56% (16% grade III-IV). OS 54%.

February 2013-October 2015: prospective observational study in 213 consecutive adult patients who received allo-HSCT for high-risk hematological malignancies (AL 56%, CR 41%, DRI high/very high 56%).

Greco R et al. In preparation
HHV6 Specific T-Cells Are Predictive Biomarker of Active HHV6 Infection

HHV6-specific T-cells were higher in HHV6 reactivating patients \((p=0.0149; \ n=43.48\) per \(10^5\ PBMC\)) than in non-reactivating patients \((n=12.57\) per \(10^5\ PBMC\)), especially in presence of active and clinically relevant HHV6 infection \((p<0.0001; \ n=81.46\) per \(10^5\ PBMC\)).

**CONCLUSIONS**

- Polyclonal immune reconstitution biomarkers were not sufficient to predict clinically relevant HHV6 infection.

- Reconstitution of functional HHV6 immunity is able to predict subsequent severe clinical manifestations:
  - Fine tune anti-viral treatment of patients
  - Improved risk stratification
  - Better patient management, fewer toxic side-effects
  - Significant potential cost savings on anti-viral drugs

**FUTURE PLANS**

- To validate the thresholds of HHV6-specific IFN-g spots as a surrogate marker in larger prospective trials.

- To standardize the IFN-g ELISpot protocol.
Transplant recipients are prone to a spectrum of neurological disorders including encephalopathy, seizures, infections, stroke, CPM, neuromuscular disorders, and CNS malignancies.

These complications may result from GVHD, radiation, chemotherapy, immunosuppressants, surgery as well as from a clinical and neuro-infectious etiology.

Definitive etiological diagnosis frequently presents a challenge due to a relative low specificity of neuroimaging studies, warranting a tissue biopsy.

Management is focused on mitigating neurological injury by careful consideration of risk versus benefit ratio of immune suppressive regimens, and therapies directed to specific etiologies.