



Transatlantic Workshop: Drug-Related Progressive Multifocal Leukoencephalopathy

The risk in transplanted patients

Marco Tuccori, PhD University Hospital of Pisa Pisa, Italy

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EPIDEMIOLOGY



AIDS/HIV+: 80% Haematological tumours: 13% Transplant recipients: 5% Auto-immune diseases: 3%

IR in HSCT: 35.4 (95%CI: 0.90-197-29) per 100.000 person/years IR in solid organ transplantation: 0 (0.00-26.81) per 100.000 person/years

Armen et al., Neurology 2010;75:1326-32

CASE REVIEW: selection criteria



transplant)

Database/Browser: MEDLINE (PUBMED) Time: from January 1970 to June 2011 Language: English

Selection keywords: ("progressive multifocal leukoencephalopathy" AND transplantation) OR ("progressive multifocal leukoencephalopathy" AND

Inclusion criteria:

a) Patient receiving organ/tissue/cell transplant
identifiable by age and gender
b) Diagnosis of progressive multifocal leukoencephalopaty

(at least on the basis of MRI)





HEMATOPOIETIC STEM CELLS: SUMMARY



24 patients (12 males, median age: 42y, range 3m – 63y): 15 died, 9 alive

Median time from HSCT to PML onset : 8.5 months (range: 1-60)

Median time from PML onset to death: 2 months (range 1-7)

HEMATOPOIETIC STEM CELLS: DISEASES and TREATMENTS



DISEASES: NHL (4), HL (4), MCL (3), AML (3), CML (3), DLBCL (1), PTCL (1), WAS (1), ALL (1), MM (1)

PREVIOUS LINES OF CHEMOTHERAPY: 27 different drugs - most frequently reported: vincristine: 7 (vinca alkaloids: 11); dexamethasone : 5 (glucocorticoids: 10); cyclophosphamide: 5; cytarabine: 5; etoposide: 5; doxorubicin: 4 (antracyclines: 7) Refractory/Relapsed: 12

ALLOGENEIC HSCT: 12 (8 GVHD); AUTOLOGOUS HSCT: 11 MYELOABLATIVE: 16; NON MYELOABLATIVE: 4; UNKNOWN: 3 CONDITIONING REGIMENS: Cyclophosphamide (14), etoposide (8), carmustine (6), melphalan (5), cytarabine (4), fludarabine (4), busulfan (2) (TBI: 10)

POST-TRANSPLANTATION THERAPY: Cyclosporine (6), MTX (6), tacrolimus (4), rituximab (3), prednisone (1), mycophenolate mofetil (1)

HEMATOPIETIC STEM CELLS: PML TREATMENTS and OUTCOMES



| ANTIVIRALS | Overall | Alive | Died |
|-------------|---------|-------|------|
| Cidofovir | 8 | 2 | 6 |
| Cytarabine | 6 | 3 | 3 |
| Risperidone | 3 | 1 | 2 |
| Citalopram | 2 | 2 | 0 |
| Mefloquine | 2 | 2 | 0 |
| Mirtazapine | 1 | 0 | 1 |
| Ziprasidone | 1 | 0 | 1 |

| IMMUNE RECONSTITUTION | Overall | Alive | Died | GVHD |
|---|---------|-------|------|------|
| Immunosuppressants reduced or stopped | 5 | 2 | 3 | 4 |
| IL-2 | б | 3 | 3 | 1 |
| Donor-related JCV-specific CTL preparations | 1 | 1 | 0 | 0 |
| COMBINATIONS | Overall | Alive | Died | GVHD |
| Antiviral + immune reconstitution | 5 | 2 | 3 | 3 |

KIDNEY: SUMMARY





20 patients (14 males, median age: 44y, range 16y – 68y): 14 died, 6 alive

Median time from TX to PML onset: 29 months (range: 5-240) Median time from PML onset to death: 2.75 months (range 0.5-14) 13 cases published before 1990

KIDNEY: IMMUNOSUPRESSANT TREATMENTS

DRUGS: Prednisone (18); azathioprine (16); mycophenolate mofetil (5); cyclosporine (3); cyclophosphamide (3); methylprednisolone (2); bleomycin (1), melphalan (1), basiliximab (1), tacrolimus (1), sirolimus (1)

• IR in MMF users 14.4 cases per 100.000 person/years at risk vs 0 in MMF-non-users (p=0.11).

• Risk factors (PML vs non-PML, p< 0.05): BK virus infection (22.2% vs 1.1%), post-transplantation transfusion (75% vs 34%), use of antirejection medications in the first year (56% vs 14%)

Source: United States Renal Data System (Neff et al., Transplantion 2008;86:1474)



| ANTIVIRALS | Overall | Alive | Died |
|-----------------------|---------|-------|------|
| Cidofovir | 1 | 1 | 0 |
| Cytarabine | 2 | 2 | 0 |
| Ganciclovir | 1 | 0 | 1 |
| No treatment reported | 12 | 0 | 12 |

| IMMUNE RECONSTITUTION | Overall | Alive | Died | Rejection |
|---------------------------------------|---------|-------|------|-----------|
| Immunosuppressants reduced or stopped | 8 | 6 | 2 | 5 |

| COMBINATIONS | Overall | Alive | Died | Rejection |
|--------------------------------------|---------|-------|------|-----------|
| Antiviral + immune reconstitution | 4 | 3 | 1 | 1 |

- 8 patients (7 females, median age: 57y, range 39y 71y): 7 died, 1 alive
- Median time from TX to PML onset: 10.5 months (range: 0.25-120)
- Median time from PML onset to death: 2.75 months (range 4.5-18)

LIVER: IMMUNOSUPRESSANT TREATMENTS

- **DRUGS (TX):** Cyclosporine (5); prednisolone (4), azathioprine (3), mycophenolate mofetil (3), basiliximab (1)
- DRUGS (rejection, 2 cases): Methylprednisolone (2), tacrolimus (2), muromonab-CD3 (1)







| ANTIVIRALS | Overall | Alive | Died |
|-----------------------|---------|-------|------|
| Cidofovir | 1 | 0 | 1 |
| Cytarabine | 3 | 1 | 2 |
| No treatment reported | 2 | 0 | 2 |

| IMMUNE RECONSTITUTION | Overall | Alive | Died | Rejection |
|--------------------------------------|---------|-------|------|-----------|
| Immunosuppressant reduced or stopped | 5 | 1 | 4 | 1 |

| COMBINATIONS | Overall | Alive | Died | Rejection |
|--------------------------------------|---------|-------|------|-----------|
| Antiviral + immune reconstitution | 4 | 1 | 3 | 1 |

HEART: SUMMARY

- 4 patients (4 males, median age: 59y, range 49y 68y): 4 died
- Median time from TX to PML onset : 42 months (range: 24-57)
- Median time from PML onset to death : 0.63 months (range 0.5-2)
- 3 cases published before 1991

HEART: IMMUNOSUPRESSIVE TREATMENTS

DRUGS: Cyclosporine (4); prednisone (4), azathioprine (3), mycophenolate mofetil (1), sirolimus (1)

HEART: PML TREATMENTS and OUTCOMES

| Treatments | Overall | Alive | Died |
|-----------------------|---------|-------|------|
| Acyclovir | 1 | 0 | 1 |
| No treatment reported | 3 | 0 | 3 |

NO ATTEMPTS OF IMMUNE RECONSTITUTION







LUNG: SUMMARY

- 2 patients (2 males, age: 43y and 55y): 1 died, 1 alive
- Time to PML diagnosis from TX: 15 and 7 months
- Time to death from PML symptoms: 15 months
- Transplantation received for pulmonary fibrosis and bronchiectasis

LUNG: IMMUNOSUPRESSANT TREATMENTS

DRUGS: Azathioprine (2), prednisone (2), mycophenolate mofetil (2), cyclosporine (1)

LUNG: PML TREATMENTS and OUTCOMES

| Treatments | Overall | Alive | Died |
|--------------------------|---------|-------|------|
| Cidofovir + IS reduction | 1 | 1 | 0 |
| IS reduction only | 1 | 0 | 1 |

NO CASES OF REJECTION





BOWEL: SUMMARY

- 1 patient (female, age: 34): died
- Time from TX to PML onset: 15 months
- Time from PML onset to death: NA
- Received transplantation for Gardner's syndrome

BOWEL: IMMUNOSUPRESSANT TREATMENTS

DRUGS: Tacrolimus, unspecified corticosteroids

BOWEL: PML TREATMENTS and OUTCOMES

NO TREATMENTS REPORTED









CONCLUSIONS



- PML has been reported both in HSCTs and solid organ transplantations with different immunosuppressants. The attribution/quantification of specific causative roles to single drugs remain a hard challenge.
- In patients receiving HSCT, the timeframe from transplantation to PML onset is particularly short as compared to that of solid transplantation recipients, probably due to a high degree of immunosuppression caused by exposure to previous antineoplastic chemotherapies.
- The reduced intensity conditioning in HSCT patients by nonmyeloablative regimens, developed to reduce the risk of adverse reactions to immunosuppressive drugs, has been also associated with PML cases.
- Treatment of PML by discontinuation of immunosuppressive therapy (probably the best available therapeutic approach) has been related to episodes of GVHD or transplant rejection, although the risk for these events remains undetermined.



Prof. Corrado Blandizzi Dr. Daniele Focosi Dr. Sabrina Montagnani Dr. Stefania Mantarro Dr. Giulio Giustarini Dr. Luca Antonioli Dr. Matteo Fornai



THANK YOU FOR YOUR KIND ATTENTION!