OSPEDALE SAN RAFFAELE

A commentary on Persistent Low Level Mixed Chimerism in SAA

Maria Teresa Lupo-Stanghellini, MD
BMT-Unit
OSR – Milano

Emopatie non Maligne e Trapianto,
Napoli, January 24th - 25th 2017

Mixed Chimerism

1. Individuals who exhibited a donor profile by STR-PCR analysis with no evidence of recipient cells at any time post BMT were referred to as donor chimeras (**DC**).

2. Individuals who exhibited a mixed population of donor and recipient cells but who subsequently reverted to complete donor chimerism by one-year post-BMT were referred to as transient mixed chimeras (**tMC**).

3. Mixed chimeras two distinct patterns:
    - stable mixed chimerism (**sMC**) where chimerism kinetics indicated <5% fluctuation in the percentage of recipient cells over time
    - progressive mixed chimerism (**pMC**)where chimerism kinetics indicated =/>15% rise in the percentage of recipient cells over a 3-month analysis period

4. Recipient chimeras (**RC**) with primary graft rejection

Lawler M, BJH 2008

Mixed Chimerism

Multiple meanings

- Increasing MC levels in HSCT performed after hematological malignancies may indicate
  - ✓ Disease relapse,
  - ✓ Graft failure
  - ✓ Rejection
  - ✓ …
- Decreasing of MC (after IST tapering or DLI) may be early predictor of GvHD (but not always GvL).
- MC may remain stable indicating a tolerant state associated with low incidence of GvHD.

Multiple clinical implications

May occur in different cellular compartments

- Lymphocytes (CD4 / CD8 / B cells / NK cells)
- Granulocytes

Different techniques

- STR-PCR
- digital droplet PCR

May have varying course over time

Mixed Chimerism - thalassemia

MC level 1 (donor>90%),
MC level 2 (90%>donor>75%)
MC level 3 (donor<75%)

Risk of rejection in MC level 1 is low, it is higher in level 2–3 MC.

Table 2 Evolution of mixed chimerism from 2 to 24 months after BMT, based on the second month engraftment status

	Graft status at 2 months	*vs*	*Graft status at 12 months*			*Graft status at 24 months*		
			Persistent MC	*Rejection*	*Complete engraftment*	*Persistent MC*	*Rejection*	*Complete engraftment*
Complete engraftment	200 pts (67.8%)	→	9 pts (4.5%)	—	191 pts (95.5%)	6 pts (3%)	—	194 pts (97%)
MC level 1	55 pts (18.6%)	→	20 pts (36.3%)	4 pts (7.2%)	31 pts (56.3%)	15 pts (27.2%)	7 pts (12.7%)	33 pts (60%)
MC level 2	21 pts (7.1%)	→	6 pts (28.5%)	8 pts (38.1%)	7 pts (33.3%)	4 pts (19%)	8 pts (38.1%)	9 pts (42.8%)
MC level 3	19 pts (6.47%)	→	3 pts (15.7%)	16 pts (84.2%)	—	1 pt (5.2%)	18 pts (94.7%)	—

MC level 1: presence of residual host cells (RHCs) <10%; MC level 2: presence of RHCs = 10%/25%; MC level 3: presence of RHCs >25%.

Andreani M, BMT 2000

Mixed Chimerism - thalassemia

At two years post-HSCT, the majority of patients either rejected their grafts or converted to full donor chimerism, while 19–27% had persistent MC.
These patients remained transfusion-free from 2 to 11 years post-transplant

There is no consensus on treatment of MC in these patients.

A watch-and-wait approach leads to full graft rejection with relapse of transfusion-dependent thalassemia in the majority of patients, although cases of persistent and stable MC have been described.

Alternatively, a modulation of the donor immune system:
escalating immunosuppression;
increasing the donor-versus-host alloimmunity (rapid discontinuation of IST or DLI)

Caveat…. **GvHD**!!!!
Caveat… how long is a safe long term follow-up? **Critical time threshold**?

Mixed Chimerism - SAA

1. Individuals who exhibited a donor profile by STR-PCR analysis with no evidence of recipient cells at any time post BMT were referred to as donor chimeras (**DC**).

2. Individuals who exhibited a mixed population of donor and recipient cells but who subsequently reverted to complete donor chimerism by one-year post-BMT were referred to as transient mixed chimeras (**tMC**).

3. Mixed chimeras two distinct patterns:
    - stable mixed chimerism (**sMC**) where chimerism kinetics indicated <5% fluctuation in the percentage of recipient cells over time
    - progressive mixed chimerism (**pMC**)where chimerism kinetics indicated =/>15% rise in the percentage of recipient cells over a 3-month analysis period

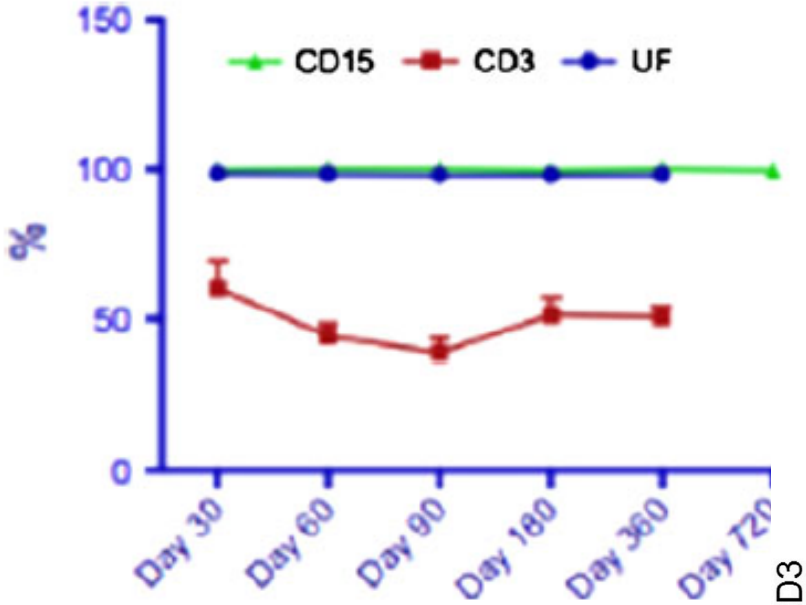
4. Recipient chimeras **(RC)** with primary graft rejection

Patients who were **DC / tMC / sMC did not experience graft rejection.**
Patients who were initially either DC or low level mixed chimeras but who subsequently showed **elevations =/>15% in the level of recipient cells in serial samples were at high risk of graft rejection.**

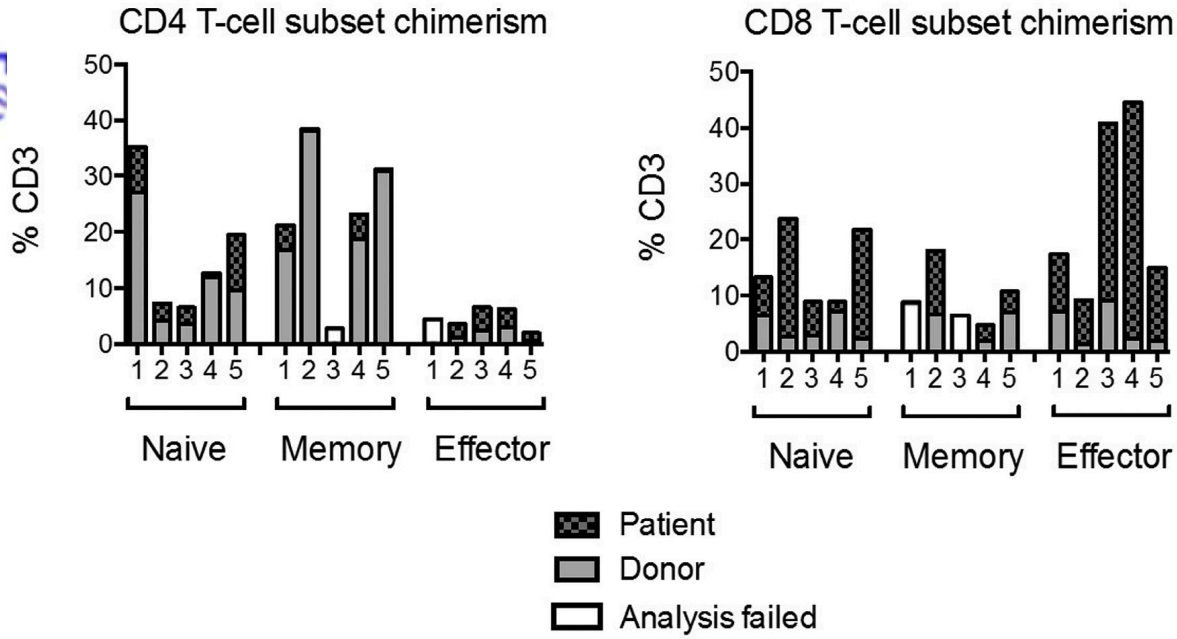
Lawler M, BJH 2008

Mixed Chimerism - SAA

Alemtuzumab appears to induce **tolerance** post-HSCT with the findings of **stable mixed T cell chimerism** with **full donor myeloid chimerism** and the **absence of chronic GVHD**, and which persist on withdrawal of post-graft immunosuppression.



Grimaldi F, BBMT 2017
Gandhi S, Int J Hematol 2013
Marsh JC, Blood 2011



Mixed Chimerism

A significant proportion of transplanted patients can develop a long-term and stable mixed chimerism, complete donor engraftment is not essential for sustained hematopoiesis.

Madden LM, BBMT 2016
Kropshofer G, Am J Hematol, 2016

Mixed Chimerism - SAA

Consider routine testing for chimerism analysis post-SCT

✓ +1, (+2), +3, +6 (+9) and +12 months post-SCT.

Chimeric analysis prior to the commencement of withdrawal of immunosuppression.
Serial monitoring during withdrawal of immunosuppression.
→ Tapering of CyA should be accompanied by chimerism assessment.
✓ Chimerism evaluation every 6-12 months

Chimerism analysis is recommended following allogeneic SCT for SAA and FA, providing valuable laboratory information on engraftment and the risk of early and late graft rejection, particularly in the context of withdrawal of immunosuppression.

Always consider the peculiarity of conditioning regimen!
✓ FLU Cy Campath vs FLU Cy ATG TBI200