Upfront HSCT with an Alemtuzumab Based Conditioning Regimen in Children with Acquired Aplastic Anemia: A Retrospective Study from the SFGM-TC

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Introduction

- Aquired Aplastic Anemia : 2 case / million // 15 pediatrics diagnostic / year
- Gold standard treatment is hematopoietic stem cell transplantation if matched donor. If not immunosuppressive therapy (IST) with horse antithymocyte globulin and ciclosporine.
- Probleme with IST
  - Efficacity for 60-70% but EFS low at 45% (OS 5 ans 90%)
  - 2em ligne treatment : HSCT with EFS 74%
  - Even if initial efficacity : risk of relpase ; ciclo-dependance ; clonal evolution ; no so good quality of life

Epidemiology of aplastic anemia in France: a prospective multicentric study. The French Cooperative Group for Epidemiological Study of Aplastic Anemia ; Mary JY, Baumelou E, Guiguet M.. Blood 1990; 75(8):1646-1653.
Long-Term Follow-up of the Randomized Controlled Study in Patients with Newly Diagnosed Severe Aplastic Anemia Treated with ATG, Cyclosporine, with or without G-CSF: On Behalf of the SAA Working Party of the EBMT. Tichelli A, Peffault de Latour R, Passweg J et al. Haematologica, 2020 May;105(5):1223-1231.
Excellent outcome of matched unrelated donor transplantation in paediatric aplastic anaemia following failure with immunosuppressive therapy: a United Kingdom multicentre retrospective experience. Br J Haematol. 2012;157(3): 339-346. Samarasinghe S, Steward C, Hiwarkar P, et al.

HSCT for Aquired Aplastic Anemia

- Matched related HSCT excellent historic result EFS 2 years 87%
- Dufour et al. 44 successive children who received a matched unrelated donor (MUD), hematopoietic stem cell transplantation (HSCT), there was an excellent estimated 5-year EFS of 95% (44/40 after IST). Alemtuzumab based conditioning with fludarabine and cyclophosphamide.
- In 2005 to 2014, UK cohort of 29 children with idiopathic AA thus received MUD HSCTs as **first-line therapy** :

- Outcomes for the up-front unrelated cohort HSCT were similar to Matched Related Donor HSCT EFS 2 years 92% vs 87%. 1 graft rejection and 1 died (pneumopathie)

- French Study MUD UPFRONT

Excellent outcome of matched unrelated donor transplantation in paediatric aplastic anaemia following failure with immunosuppressive therapy: a United Kingdom multicentre retrospective experience. Samarasinghe S et al. Br J Haematol. 2012

Outcome of aplastic anaemia in children. A study by thesevere aplastic anaemia and paediatric disease working partiesof the European group blood and bone marrow transplant Dufour et al. Br J Haematoll, 2015

Similar outcome of upfront-unrelated and matched sibling stem cell transplantation. Dufour et al. Br J Haematol - 2015

Why Alemtuzumab ?

- causes lymphocyte lysis by binding to the glycoprotein CD52, a highly expressed non-modulatory antigen present on the surface of virtually all B and T lymphocytes, as well as monocytes, thymocytes, and macrophages
- Principal objective : Limit GVH disease
    - UK cohort of 29 children :
        - The 1-year CI of grade II–IV acute GVHD was 10 +/- 6 %; there was only one case of grade III/IV acute GVHD (frequency of 3+/- 5%; in one patient receiving a MUD HSCT) requiring systemic immunosuppressive with steroids. The rest were treated with topical steroid therapy.
        - The 1-year CI of chronic GVHD was 19 +/- 8% (occurring in 5 of the 29 cases for a frequency of 17+/-2%, 4 receiving MUD and 1 MMUD HSCTs). Chronic GVHD was limited in all cases and restricted to skin and required topical therapy only.
    - Retrospective national UK study compared the use of alemtuzumab-based conditioning regimens for hematopoietic SCT (HSCT) in acquired severe aplastic anemia with antithymocyte globulin (ATG)-based regimens (100 patients analysed).
        - Lower risk of chronic GVHD (cGVHD) was observed in the alemtuzumab group (11% vs 26%, P=0.031).

Alemtuzumab with fludarabine and cyclophosphamide reduces chronic graft-versus-host disease after allogeneic stem cell transplantation for acquired aplastic anemia Judith Cet al. Blood 2011

Retrospective study of alemtuzumab vs ATG-based conditioning without irradiation for unrelated and matched sibling donor transplants in acquired severe aplastic anemia: a study from the British Society for Blood and Marrow

Objective of the study

- Analyse the clinical and biological data of all the children (<18 years at time of HSCT) with an acquired AA transplanted in first line with a MUD and after an FCC conditioning in the SFGM Tc center.
- extracted from the data base of the SFGM Tc.

Results
Patient characteristics

Retrospective study
20 children included treated in 9 centers of the SFGM Tc
Confirmation of acquired aplastic anemia (50% HPN clone ; for the other normal telomere + NGS aplasia (8/10) + fanconia test normal

Conditionning : Campath 0.9 mg/kg
Cyclophosphamide 120 mg/kg
Fludarabine 150 mg/m2
GVH prophylaxie : Ciclosporine alone
Rituximab: 5 patients at Day 5

Source of cells
Bone Marrow 19 patients (95%)
PBSC 1 patient (5%)

TNC x 10*7 median [IQR] 4.5 [2.9-5.4]

Variables	Modalities	N=20 (%)
Patient sex	F	8 (40)
	M	12 (60)
Age at diag	median [IQR]	9.9 [6.8-12.4]
Age at HSCT	median [IQR]	10.4 [7.3-12.6]
Severity	severe	12 (60)
	very severe	8 (40)
Months between diag and HSCT	median [IQR]	2.8 [2.2-3.3]
	(range)	(1.5-8.2)

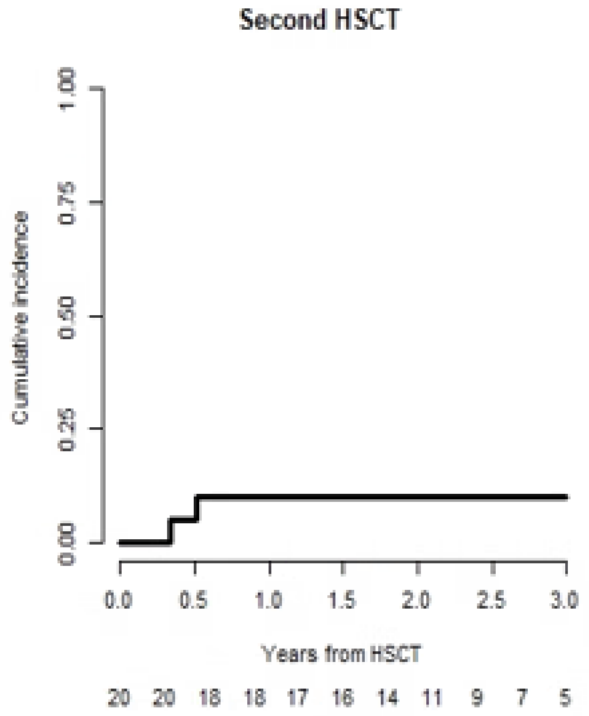
Survie and Engraftment

- All patient are alive with median follow up 2.5 years (1.8 – 3.1)

- Median time to engraftment :
  - Neutrophils 23 days IQR (19-29)
  - Platelets 29 days IQR (17-35)

Reject and graft dysfunction

- No primary graft failure
- 3 patients experimented secondary graft failure at day 40, 43 and 51
  - Two had autologous reconstitution and are alive with good hematological function 2.7 and 6.4 years later (at last follow up donor blood chimerism were 3% and 25% respectively; none developed PNH or malignancy at last FU).
  - 1 need second transplant with good evolution 6.2 years after the second transplant (4 months between the 2 grafts)
- 1 patient experimented poor graft function and need second transplant 6 months after the first with good evolution (2 years after)
- The 2 years second HSCT incidence was 10%



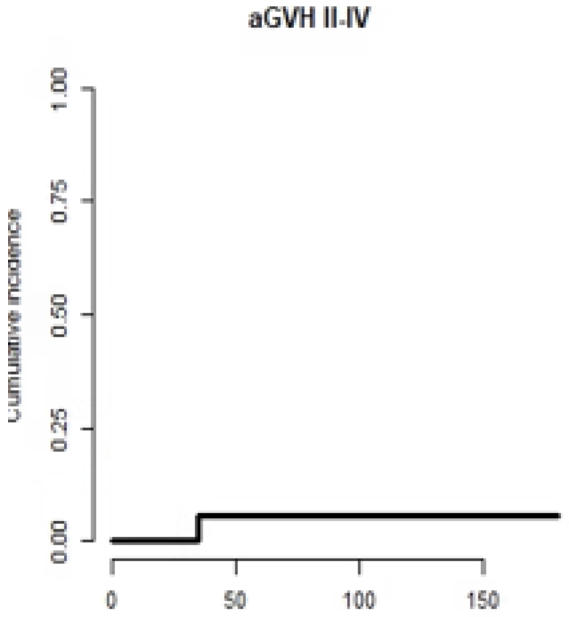
GVH

Cumulative incidence (CInc) of acute GvHD were 5.6% at Days 100 without grade 3-4

Two patients experienced skin acute GvHD with good evolution

1 patient grade I treated by steroid topic

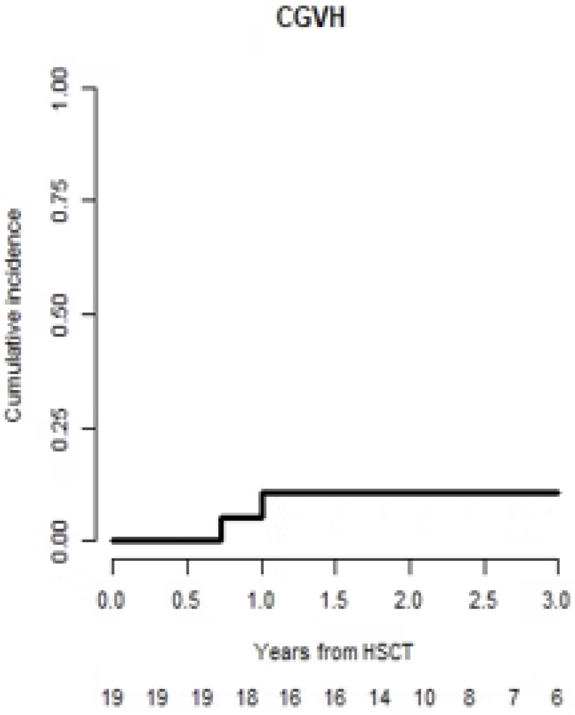
1 patient grade II treated with corticosteroid systemic during 3 months



Cumulative incidence (CInc) of chronic GvHD were 10.5% at 2 years

without extensive chronic GvHD.

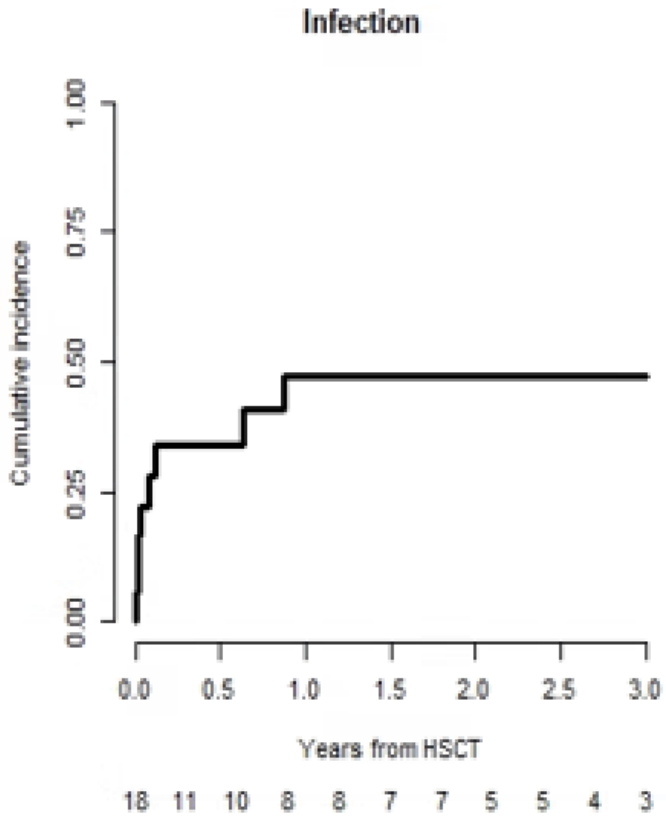
Only one patient required Ruxolitinib treatment for chronic GvHD of the skin (mild stage with eczema at the elbow) with good evolution. At the last follow up the patient take Ruxolitinib and the neoral is in decreasing



Infections

Septicemie
6 episodes (3 strepto / 2 staph / 1 E. coli) (30% of the patients)
1 transfert in USC for hypoxemia pneumopathie

Viral complication
1 ADV dissemination with reanimation. Good evolution after CTL anti ADV and second transplantation
4 EBV reactivation with good evolution after RITUXIMAB (without PTLD)
mean time 7.5 months



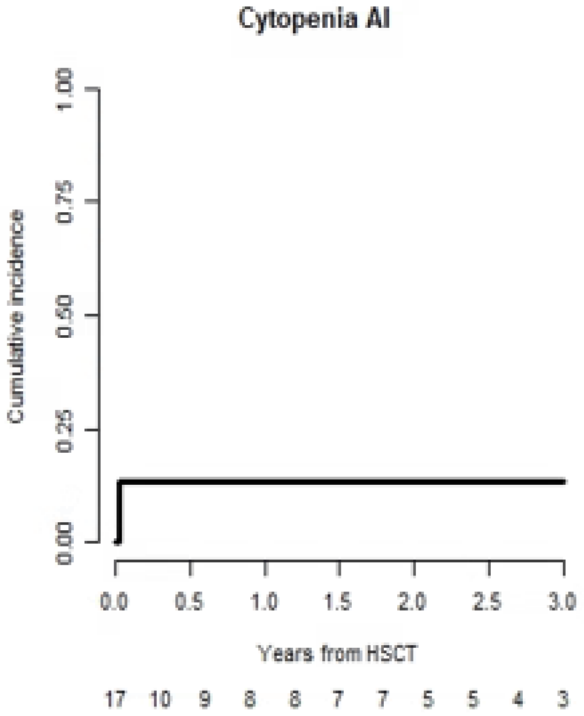
Auto-immune hemolytic anemia

Two patients developed at days 33 and 287 post HSCT = cumulative incidence of 11.8%.

First line treatment corticotherapy + Rituximab

One need a 2 line of treatment with Bortezomib to achieve response.

At the last FU, they are in remission one without IS and one with cyclosporine alone



Auto-immunity

- One patient developed an inflammatory bowel disease need anti TNF 18 months after the HSCT
- One patient an hashimoto thyroiditis 13 months after the HSCT

Last Follow up

- All patient are alive with good hematologic reconstitution
- 2 patients with autologous reconstitution (90%)
- 2 patients are treated with immunosuppressive (10%)

Discussion

- Alemtuzumab in combination with Fludarabine and Cyclophosphamide (FCC) in unrelated donor HSCT for acquired AA is associated with a very low risk of chronic GVHD (5%), a low risk and low grade of acute GVHD (10%, and all cases grade I or II) and OS (100%).

- The EFS is excellent 83.6% at 2 years compare the patient treat with IST in frontline (EFS 45%)

Comparaison with historic study

Study	SFGM Tc groupe	Dufour et al upfront	MSD historic	HSCT second line
Country	France	UK	UK	UK
Period	2013-2023	2005-2014	-	2000-2009
Number of patient	20	29	87	24
mean age (years)	10.4	8.9	8.9	9.6
OS (%)	100	96	91	74
EFS (%)	83.4	92	87	74
Graft Failure (%)	20	4	1	-
Delay diagnostic/HSCT (months)	2.8	4.5	4.5	12

Autoimmune cytopenias (AIC) following allogeneic haematopoietic stem cell transplant for acquired aplastic anaemia: a joint study of the Autoimmune Diseases and Severe Aplastic Anaemia Working Parties (ADWP/SAAWP) of the European Society for Blood and Marrow Transplantation (EBMT) Dufour et al.

- Retrospective study incidence of autoimmune cytopenia (AIC) in 530 paediatric and adult patients with acquired aplastic anaemia (aAA) who underwent first allogeneic HSCT between 2002 and 2012.
- Twenty-five patients (4.7%) were diagnosed with AIC at a median of 10.6 (2.6–91.5) months post HSCT :

8 patients were diagnosed with immune thrombocytopenia ; 7 with autoimmune haemolytic anaemia ; 7 with Evans syndrome ; 4 with auto-immune neutropenia

- Risk factor : PBSC vs BM // ATG vs Alemtuzumab : incidence identique //
- AIC was a rare complication with a cumulative incidence of AIC at 1 and 10 years post HSCT of 2.5% (1.2–3.9 95% CI) and 5.1% (3.1–7.2 95% CI).

Clinical Study

Autoimmune Complications after Hematopoietic Stem Cell Transplantation in Children with Nonmalignant Disorders

- Study of 92 children treated with HSCT Between 2000 and 2012
- 51 with congenital hemoglobinopathies, 19 with primary immunodeficiency disease, 10 with metabolic disorders, five with Fanconi anemia, three with aplastic anemia, and four with familial hemophagocytic lymphohistiocytosis.
- Results : six (6.5%) with autoimmune hemolytic anemia (AIHA), six (6.5%) with idiopathic thrombocytopenia, three (3.3%) with mild leucopenia, two (2.2%) with aplastic anemia, two (2.2%) with autoimmune thyroid disease, and one (1.1%) with autoimmune hepatitis.

Thyroidite and Alemtuzumab

- Approximately 20% of patients who received alemtuzumab for multiple sclerosis developed auto immune thyroidite upon recovery of lymphocyte counts.
- Prospectively studied 26 patients with symptomatic SCD who received a busulfan, fludarabine, and alemtuzumab conditioning regimen followed by alloHCT. Of these 26 patients, three (12%) developed autoimmune thyroid disease after alloHCT.
- In our review to date, there have been no published cases of auto-immune thyroid disease after treatment with alemtuzumab and alloHCT in pediatric patients.

Autoimmune Thyroid Disease Following Alemtuzumab Therapy and Hematopoietic Cell Transplantation in Pediatric Patients with Sickle Cell Disease. Kristen M et al. Pediatr Blood Cancer 2014.

Limite

- retrospective study / exhaustive ?
- probleme of graft failure and auto immunity
- Interest of comparison with MUD UPFRONT

CONCLUSION

HSCT upfront for treatment of Acquired Aplastic Anemia is good option

More study are necessary for determine the best conditioning

Merci

- Flore Sicre
- à tout les centres ayant participé à l’étude
- au centre de réference pour sa confiance
- à tous pour votre attention !