Actualités dans la prise en charge de l’aplasie médullaire

Régis Peffault de Latour, MD, PhD

French reference center for aplastic anemia & PNH
French network for rare immunological & hematological disorders (MaRIH)
Severe aplastic anemia working party of EBMT (SAAWP EBMT)
Hôpital Saint-Louis, Paris, France
Actualités dans la prise en charge de l’aplasie médullaire idiopathique

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Difference between acquired and inherited aplastic anemia?

Question #1

Diagnosis of aplastic anemia

PNH > 1%

PNH <1%

> 18 years

< 18 years

FA breakage test

Fanconi

≤10 years

> 10 years

NGS

Telomeres ± NGS

Others

Telomeropathy

Normal

Idiopathic aplastic anemia

• CBCs ≤ 2 years
• Familial history
• Normal HbF & αFP
• Normal physical exam
Difference between acquired and inherited aplastic anemia?

Question #2

**SAA**
Hypocellularity (<30%) and at least 2/3 criteria:
- PNN < 0.5x10⁹/L
- Platelets < 20x10⁹/L
- Reticulocytes < 20x10⁹/L

**VSAA**
- PNN < 0.2x10⁹/L

**Moderate**
- Not all criteria for SAA
- PNN > 0.5x10⁹/L

Transfusions?
- Yes
- No

Treatment

Follow-up

Camitta BM et al. Blood 1976;48:63–70; SAA, severe AA; VSAA, very severe AA
Idiopathic aplastic anemia needed to be treated

- HLA-identical sibling donor and age < 40
  - HSCT
  - Marrow / Cy + ATG / CSA MTX

- No sibling donor or age 40 or more
  - hATG + CSA
  - Refractory/relapse
  - 10/10 (8/8 matched UD)
    - Young (<30 years)
      - First year
        - YES: Unrelated matched BMT
        - NO: Eltrombopag
          Repeated IST
          Alternative (mismatch BMT)

Question #3

Treatment (guidelines & update)

YES: Unrelated matched BMT

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Unrelated matched BMT

Refractory/relapse

Eltrombopag Repeated IST

 alternative (mismatch BMT)
Up-front MUD transplantation
Experimental approach

PHRC National 2019 / PI: JH Dalle (<18 years) & R Peffault de Latour

Essai de phase II évaluant la faisabilité de réaliser une allogreffe à partir après d’un donor non apparenté HLA 10/10 en première intention chez des enfants atteints d’aplasies médullaires idiopathiques

> Endpoint primaire et nombre de patients requis:
  • Réalisation de l’allogreffe dans les 60 jours après identification du donneur 10/10
  • 25 patients (36 mois /24 mois de suivi), <18 ans, analyse intermédiaire 12 pts
Treatment (guidelines)

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Horse ATG + Cyclosporine
The French experience – response characteristics

- **Response characteristics**
  - **Responders**
    - 40% at months 3 & 60% at months 6

Horse ATG + Cyclosporine
The French experience – response characteristics

• Response characteristics
  • Responders
    • 40% at months 3 & 60% at months 6

Horse ATG + Cyclosporine
The French experience – response characteristics

• **Response characteristics**
  • **Responders**
    • 40% at months 3 & 60% at months 6
    • Better & quicker response for patients with moderate aplastic anemia

Horse ATG + Cyclosporine
The French experience – response characteristics

• Response characteristics
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  • Complete response is exceptional (!)

Horse ATG + Cyclosporine
The French experience – response characteristics

• Response characteristics
  • Responders
    • 40% at months 3 & 60% at months 6
    • Better & quicker response for patients with moderate aplastic anemia
  • Complete response is exceptional (!)
  • Refractory patients (about 30-40%)

Any progress since 40 years?
Anti-thymocyte globuline

- Add androgens to ATG
  - No increase in response rate (Champlin, Blood 1985)
- Add to or replace ATG with megadose corticosteroids
  - No increase in response; high toxicity (Marmontl, Prog Clin Biol Res 1984)
- Replace ATG with high dose cyclophosphamide
  - Toxicity (Tisdale, Lancet 2001; Blood 2002)
- Replace ATG with moderate dose cyclophosphamide
  - Excessive toxicity secondary to neutropenia (Scheinberg, Blood 2014)
- Add mycophenolate mofetil to ATG/CsA
  - No improvement in response/survival (Scheinberg, Br J Haematol 2006)
- Add sirolimus to ATG/CsA
  - No improvement in response/survival (Scheinberg, Haematologica 2009)
- Add G-CSF to ATG/CsA
  - No improvement in response/survival (Locasciulli, Haematologica 2004)
- Prolonged CsA (2 years) to prevent relapse
  - Delayed but ultimately equivalent rate (Scheinberg, Am J Hematol 2014)
Perspectives – eltrombopag first line
Naive patients clinicaltrials.gov NCT02099747

RACE study

A prospective Randomized multicenter study comparing horse Antithymocyte globulin (hATG) + Cyclosporine A (CsA) ± Eltrombopag as front-line therapy for severe aplastic anemia patients.

PRINCIPAL INVESTIGATORS

Regis Peffault de Latour (Paris)  Antonio M Risitano (Naples)
Perspectives – eltrombopag first line
Naive patients clinicaltrials.gov NCT02099747

Primary endpoints: CR rate at 3 mo, 7% (standard IST) versus 21% (Experimental arm)
Perspectives – eltrombopag first line
Naive patients clinicaltrials.gov NCT02099747

<table>
<thead>
<tr>
<th>Country</th>
<th># sites</th>
<th># open sites</th>
<th># Randomized subjects</th>
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<tr>
<td>FR</td>
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<td>7</td>
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</tr>
<tr>
<td>NL</td>
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<td>11</td>
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<td>CH</td>
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</tr>
<tr>
<td>DE</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>28</td>
<td>205</td>
</tr>
</tbody>
</table>
Horse ATG + Cyclosporine
The French experience – response characteristics

• Response characteristics
  • Responders
    • 40% at months 3 & 60% at months 6
    • Better & quicker response for patients with moderate aplastic anemia
  • Complete response is exceptional (!)
  • Refractory patients (about 30-40%)

• Refractory patients = 2 questions:
  - Is it really acquired?
  - Clonal evolution?

Treatment (guidelines)

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Marrow / Cy + ATG / CSA MTX

No sibling donor or age 40 or more

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Refractory/relapse

10/10 (8/8 matched UD)
Young (<30 years)
First year

- Yes: Unrelated matched BMT
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Repeate IST
Alternative (mismatch BMT)

Unrelated transplantation?
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TPO receptor agonist and refractory aplastic anemia
French experience - patients characteristics

• ATG-naïve patients (cohort A, n=11)
• Refractory patients (cohort B, n=35)

• Disease characteristics:

<table>
<thead>
<tr>
<th></th>
<th>Cohort A</th>
<th>Cohort B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. (%) [IQR]</td>
<td>11</td>
<td>35</td>
<td></td>
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<tr>
<td>Demographic characteristics</td>
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<tr>
<td>Age at diagnosis (y)</td>
<td>73.7 [60.9, 77.5]</td>
<td>53.4 [26.3, 67.3]</td>
<td>0.003</td>
</tr>
<tr>
<td>Age at ELT initiation (y)</td>
<td>74.1 [67.4, 78.0]</td>
<td>55.3 [35.9, 68.5]</td>
<td>0.003</td>
</tr>
<tr>
<td>Male (%)</td>
<td>4 (36.4)</td>
<td>21 (60.0)</td>
<td>0.298</td>
</tr>
<tr>
<td>Aplastic anemia characteristics</td>
<td></td>
<td></td>
<td>0.152</td>
</tr>
<tr>
<td>Idiopathic, no PHN clone</td>
<td>4 (36.4)</td>
<td>23 (65.7)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic, with PHN clone</td>
<td>6 (54.5)</td>
<td>11 (31.4)</td>
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</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>1 (9.1)</td>
<td>1 (2.9)</td>
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TPO receptor agonist and refractory aplastic anemia

French experience - main messages

• Safety
  • 1 SAE (liver toxicity)
  • Clonal evolution (lack of follow-up …)

TPO receptor agonist and refractory aplastic anemia
French experience - main messages

- **Safety**
  - 1 SAE (liver toxicity)
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- **Response rate = 40%**
  - 3 months for refractory patients
  - 6 months for 1st line
  - Multi-lineage response = 30% among responders

TPO receptor agonist and refractory aplastic anemia

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• Response rate = 40%
  • 3 months for refractory patients
  • 6 months for 1st line
  • Multi-lineage response = 30% among responders

• Of note
  • 20% of non responders responded at a higher dose (225 mg)
  • Eltrombopag can be stopped in case of robust response

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Emerging strategies: experimental transplantation

Experimental = Cord blood, MMUD and haplo

Don’t forget what supportive care can do with non-responders to IST!

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Valdez et al, CID 2011
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! Before Eltrombopag Era !

Valdez et al, CID 2011
Emerging strategies: Cord Blood transplantation

Unrelated cord blood transplantation in patients with idiopathic refractory severe aplastic anemia: a nationwide phase 2 study

- 60 day-Cuml of **neutrophil engraftment of 88.5%** with full chimerism for all of them (23/26).
- 100 day-Cuml of grade II-IV **acute GVHD was 40%** (95% CI, 20-60) (8 grade II; 0 grade III; 2 grade IV)
- 1-year Cuml of **cGVHD at 26%** (95% CI, 6-46) (severe cGvHD in 2 pts).
- 3-years **overall survival at 82%**
Emerging strategies: Haplo-identical transplantation (Post-Cy)

- **36 patients** (32 with acquired SAA and 4 with IBMF)

**Causes of death:**
- IBMF (2/4):
  - 1 infection
  - 1 GvHD
- Acquired (7/32):
  - 5 infections
  - 2 other HSCT-related

![Survival graph showing OS 74% at 2 years](image)
Haplo-empty
Experimental approach

PHRC National 2019 / Haplo-EMPTY / PI : Régis Peffault de Latour

Allogreffe haplo-identique avec injection de cyclophosphamide post-greffe chez des patients présentant une aplasie médullaire idiopathique réfractaire à un traitement immunosuppresseur

> Endpoint primaire et nombre de patients requis:
  • Taux de survie globale à 2 ans de 60% à 80% avec haplo-SCT avec PTCy.
  • 31 patients (36 mois d’inclusion / 24 mois suivi), de 3-35 ans
Conclusion
Acquired aplastic anemia in 2020

• **First line treatment in 2020**
  • Sibling transplantation: patients < 40 years
  • Horse ATG + Cyclosporine + EPAG for the others
  • Up-front MUD (experimental)

• **Refractory patients (6 months)**
  • Matched unrelated transplantation: patients < 30 years
  • Experimental transplantation: patients < 20 years (?); CB & Haplo-empty (experimental)
  • Eltrombopag for the others
Thank you!

The French Reference Center for aplastic anemia and PNH in Paris

Saint-Louis Hospital  Robert Debré Hospital  Institute of Hematology, IUH St-Louis

F Sicre, T Leblanc, JH Dalle, A Baruchel, G Socié,
N Vasquez, W. Cuccuini, J Soulier (Fanconi team),
C Kannengiesser, E Lainey, L Da Costa (Telomeres team)