

Diamond Blackfan Anemia syndrome in adult patients



Thierry LEBLANC

11^{ème} Journée du CRMR CERAMIC

Aplasies médullaires acquises & constitutionnelles

4 Octobre 2024

DBA in brief

Rare disease (5 to 7/1,000,000 live births in EU)

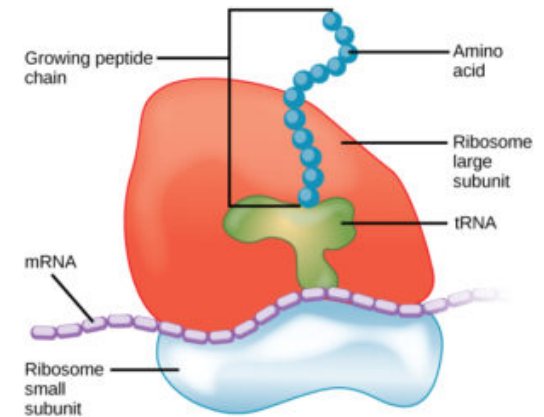
Main cause of constitutional erythroblastopenia

Ribosomopathy

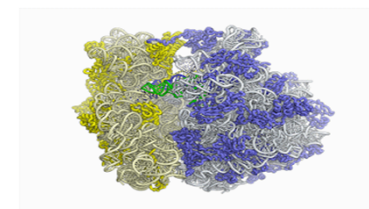
Genetic transmission: mostly AD but not so simple:

- *Problem of «silent carrier»*
- *AR & X-linked transmission also reported (rare genes)*

Very heterogeneous disease both for genetic & for clinical aspects



DBAS genes: N = 26



Gene symbol	Inheritance	Chromosome location	New protein symbol	Approximate frequency	References
DBA SYNDROME: RIBOSOMOPATHY¹					
Small ribosomal subunit (11 genes)					
<i>RPS7</i>	AD	2p	eS7	< 1%	107
<i>RPS10</i>	AD	6p	eS10	3%	54
<i>RPS15A</i>	AD	16p	uS8	<1%	108
<i>RPS17</i>	AD	15q	eS17	1%	109
<i>RPS19</i>	AD	19q	eS19	25%	110
<i>RPS20</i>	AD	8q	uS10	< 1%	57,111
<i>RPS24</i>	AD	10q	eS24	2.4%	112
<i>RPS26</i>	AD	12q	eS26	6.6%	54
<i>RPS27</i>	AD	1q	eS27	< 1%	113
<i>RPS28</i>	AD	19p	eS28	< 1%	114
<i>RPS29</i>	AD	14q	uS14	< 1%	115
Large ribosomal subunit (13 genes)					
<i>RPL4</i>	AD	15q	uL4	< 1%	116
<i>RPL5</i>	AD	1p	uL18	7%	55
<i>RPL8</i>	AD	8q	uL2	< 1%	117
<i>RPL9</i>	AD	4p	uL6	< 1%	13,54
<i>RPL11</i>	AD	1p	uL5	5%	55
<i>RPL15</i>	AD	3p	eL15	< 1%	32,118
<i>RPL17</i>	AD	18q	uL22	< 1%	15
<i>RPL18</i>	AD	19q	eL18	< 1%	119
<i>RPL26</i>	AD	17p	uL24	< 1%	120
<i>RPL27</i>	AD	17q	eL27	< 1%	113
<i>RPL31</i>	AD	12q	eL31	< 1%	42
<i>RPL35</i>	AD	3q	uL29	< 1%	119
<i>RPL35A</i>	AD	9q	eL33	3%	121
Ribosomal protein chaperones (2 genes)					
<i>TSR2</i>	X	X		< 1%	114
<i>HEATR3</i>	AR	16q		< 1%	59

Gene symbol	Inheritance	Chromosome location	New protein symbol	Approximate frequency	References
DBA SYNDROME OTHER ²					
<i>GATA1</i>	X	X		< 1%	23,122-124
<i>TP53 (GOF)</i>	AD	AD		< 1%	24,25
CANDIDATE GENES ³					
<i>RPS11</i>	AD	19q	uS17	< 1%	47
<i>RPL3</i>	AD	22q	uL3	< 1%	
<i>RPL10</i>	AD	X	uL16	< 1%	
<i>RPL10A</i>	AD	6p	uL11	< 1 %	
<i>RPL19</i>	AD	17q	eL19	< 1%	
<i>RPL34</i>	AD	4q	eL34	< 1%	
<i>RPL0</i>	AD	12q	uL10	< 1%	
GENETIC PHENOCOPIES ⁴					
<i>ADA2</i>	AR	22q11.1			27,29,43
<i>EPO</i>	AR	7q22.1			26

Most frequent genes:

***RPS19* : 25%**

***RPL5* : 7%**

***RPS26* : 6%**

***RPL11* : 5%**

Genetic diagnostic rates:

Registries : 70%

New cases : 85-90%

Wlodarski & al, Lancet Haematology 2024



Diagnosis, treatment, and surveillance of Diamond-Blackfan anaemia syndrome: international consensus statement

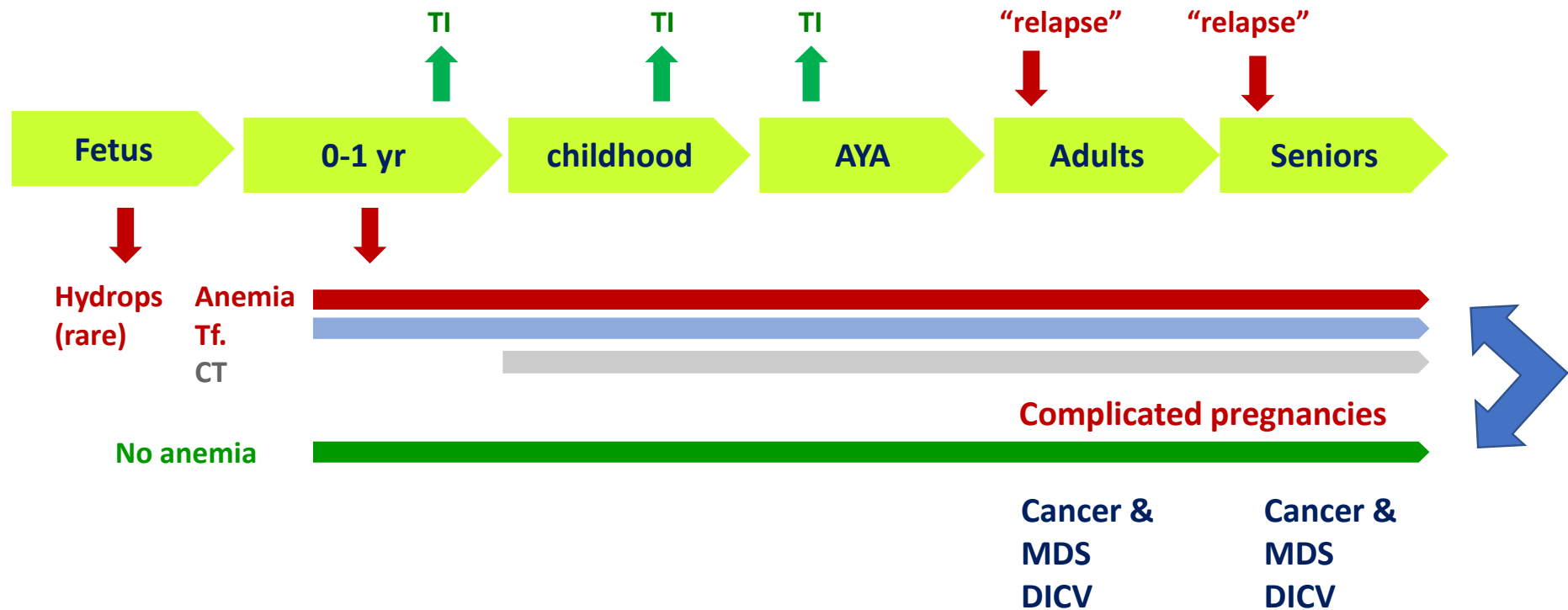
THE LANCET
Haematology

Marcin W Wlodarski, Adrianna Vlachos*, Jason E Farrar*, Lydie M Da Costa, Antonis Kattamis, Irma Dianzani, Cristina Belendez, Sule Unal, Hannah Tamary, Ramune Pasauliene, Dagmar Pospisilova, Josu de la Fuente, Deena Iskander, Lawrence Wolfe, Johnson M Liu, Akiko Shimamura, Katarzyna Albrecht, Birgitte Lausen, Anne Grete Bechensteen, Ulf Tedgard, Alexander Puzik, Paola Quarello, Ugo Ramenghi, Marije Bartels, Heinz Hengartner, Roula A Farah, Mahasen Al Saleh, Amir Ali Hamidieh, Wan Yang, Etsuro Ito, Hoon Kook, Galina Ovsyannikova, Leo Kager, Pierre-Emmanuel Gleizes, Jean-Hugues Dalle, Brigitte Strahm, Charlotte M Niemeyer, Jeffrey M Lipton*, Thierry M Leblanc*, on behalf of the international Diamond-Blackfan anaemia syndrome guideline panel†*

- ➡ **New name: DBA syndrome**
- ➡ **New criteria for diagnosis** (*versus previous guidelines: Vlachos & al, 2008*)
- ➡ **New recommendations transfusion support, chelation, corticosteroids therapy & indications for HSCT**
- ➡ **New recommendations for surveillance with special focus on cancer**

Wlodarski & al, Lancet Haematology 2024

DBAS phenotype & treatment according to age



DBAS: do not speak about « silent phenotype »?

Genetic evidence (parent with the mutation but w/o phenotype)

Biology: isolated high eADA

Graft failure

?



➡ ***New guidelines « patient **currently** w/o phenotype » who actually need the same follow-up...***

DBAS in adults: clinical presentations

Note:
CBC may be normal!

Severe or mild anemia
(macrocytosis, low
reticulocytes)

Hypo- γ -globulinemia
& CVD

Asymptomatic pts
- parent of one affected-child
- donor screening for BMT

Complicated
pregnancies

DBAS

MDS-like features
&
« true » MDS

Solid tumors,
unexpected toxicity
of chemotherapy



CASE REPORT

Adult-onset Diamond-Blackfan anemia with a novel mutation in the exon 5 of RPL11: too late and too rare

Elena Flores Ballester¹, Juan José Gil-Fernández¹, Miguel Vázquez Blanco², José M. Mesa³, Juan de Dios García³, Ana T. Tamayo¹ & Carmen Burgaleta¹

¹Department of Hematology, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain

²Department of Ophthalmology, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain

³Department of Genetics, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain

Age at diagnosis: 35 yr

Hb: 7.2 g/dL, MCV 93 fl, Rt: 13 G/L

GB: 4.3 G/L

Platelets: 342 G/L

No previous BCC available



Hematologic Landscape of Adult Patients With Diamond-Blackfan Anemia Syndrome

Nicolas Lecornec^{1,2}  | Flore Sicre de Fontbrune^{3,4}  | Edouard Forcade⁵ | Loïc Garçon⁶ | Louis Terriou⁷ | Pierre Cougoul⁸ | Karen Delavigne⁸ | Isabelle Marie⁴ | Isabelle Brindel⁴ | Éric Deconinck⁹ | Étienne Daguindau⁹ | Shanti Amé¹⁰ | Marie-Pierre Ledoux¹⁰ | Laurence Sanhes¹¹ | Stanislas Nimubona¹² | Guy Leverger¹³ | Marianne de Montalembert¹⁴  | Régis Peffault de Latour^{3,4} | Jean-Hugues Dalle¹ | Pierre Fenaux¹⁵ | Lydie Da Costa^{4,16,17,18} | Thierry Leblanc^{1,4,19,20} 

N = 235 pts adultes (> 18 ans)

Md FU from adulthood: 13 yrs

NB: median age at diagnosis for pts diagnosed during adulthood: 37.4 yr [27.3-52.5]

DBAS-specific treatment at last follow-up	220
Long-term RBC transfusions	87 (40)
None	67 (30)
Long-term steroids	48 (22)
Post-HSCT remission	11 (5)
Long-term RBC transfusions and steroids	7 (3)

Other cytopenias:

Neutropenia : 31% (< 0.5 G/L : 3%)

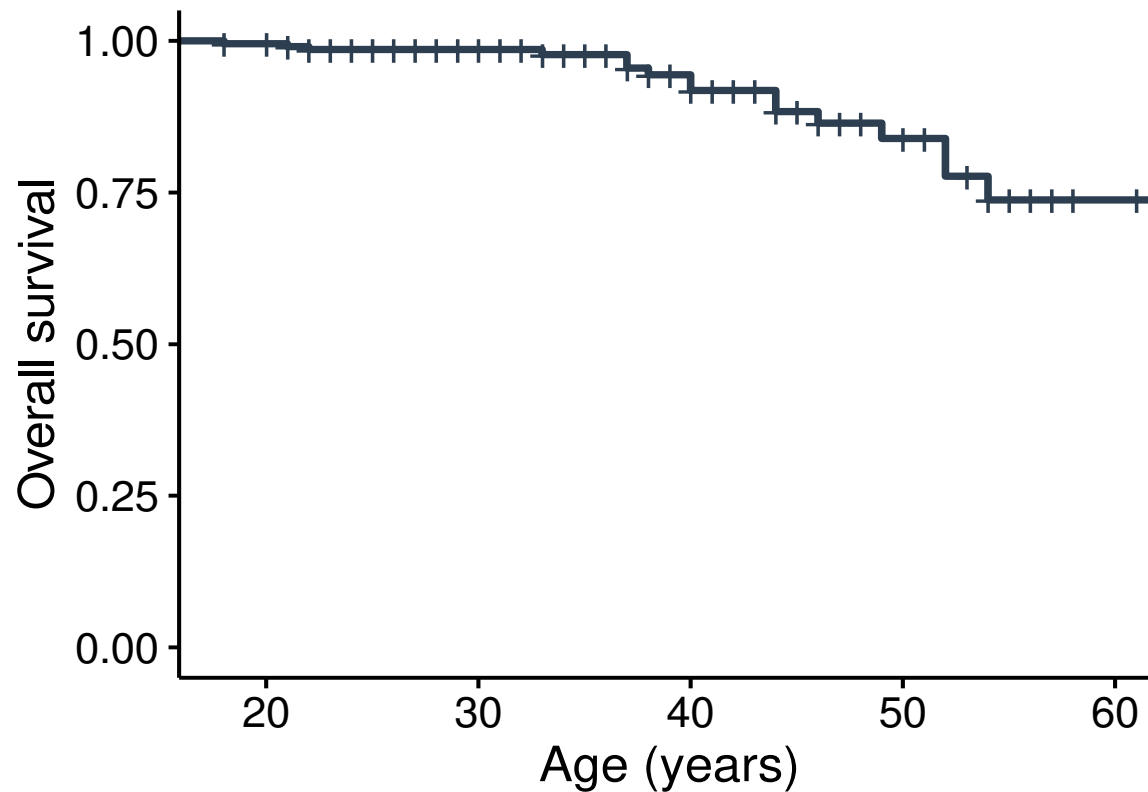
Thrombocytopenia : 15% (< 50 G/L : 3%)

To note: no case of BMF

Note: pts in TI: cohort of still “young” patients (median age: 31 yrs) : Active erythropoiesis with or w/o previous history of anemia SGR?

Denial of the disease more common at this age: low Hb but no treatment... (various level of Hb; occasional Tf in some pts)

Overall Survival (whole cohort)



OS		95% CI
28-yr	98.6%	[97-100]
38-yr	95.6%	[92-99]
48-yr	89.4%	[83-97]

Univariate analysis: only RF associated with survival: hematological malignancies

Incidence of neoplasia in Diamond Blackfan anemia: a report from the Diamond Blackfan Anemia Registry

Adrianna Vlachos,^{1,3} Philip S. Rosenberg,⁴ Eva Atsidaftos,^{1,2} Blanche P. Alter,⁵ and Jeffrey M. Lipton^{1,3}

US registry study

N = 608

FU: 9,458 person-years

Solid tumors : 15

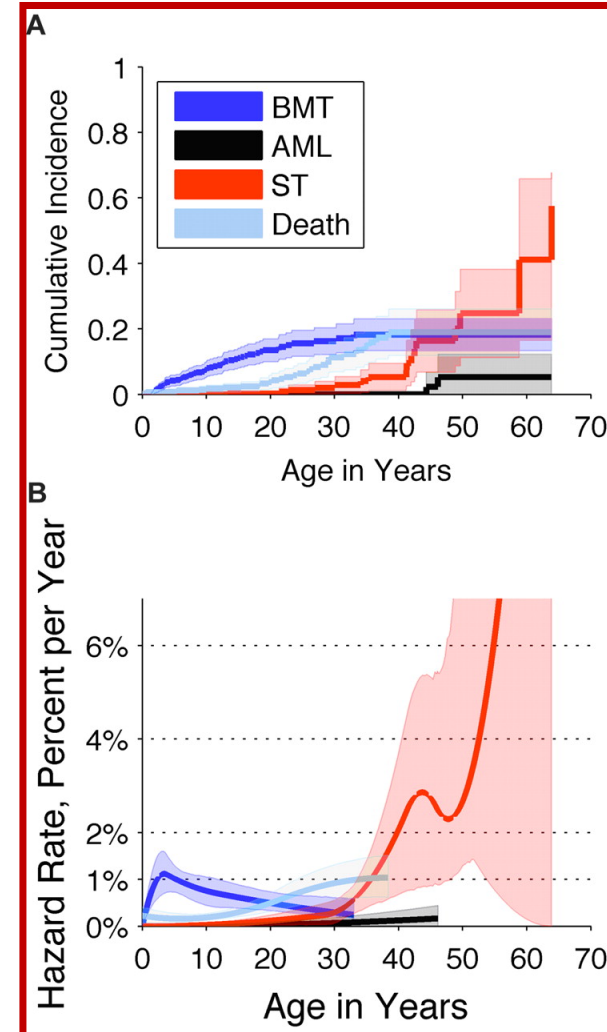
AML : 2

MDS : 2

Median age: 41 yr

**Cumulative incidence (MDS/AML+ST)
at 46 yr: 20%**

To note: various ST types



DBAS pts are at high-risk for MDS / leukemias & solid tumors

US registry: N = 608

Cancer type	No. of observed cancers	O/E Ratio	95% CI
<i>Events with significant O/E ratios</i>			
All cancers	18	5.4	3.2 - 8.6
⇒ Colon (adenocarcinoma)	3	36.2	7.5 - 105.8
⇒ Bones (osteogenic)	2	32.6	4.0 - 117.7
Female genital	3	12.0	2.5 - 35.1
AML	2	27.9	3.4 - 100.9
MDS	4	287.0	77.2 - 734.7
<i>Events with non significant O/E ratios</i>			
Oral cavity	1	15.9	0.4 - 88.3
Soft tissue sarcoma	1	9.8	0.3 - 54.8
Lung	1	8.3	0.2 - 46.4
Testis	1	8.3	0.2 - 46.1
Non-Hodgkin lymphoma	1	5.7	0.1 - 31.7
Melanoma	1	4.5	0.1 - 25.3
Breast	2	4.1	0.5 - 14.9



Problem: LDS & AML cases are poorly reviewed...

MDS & AML

O/E Ratio:

MDS: 155

AML: 55

**Note: 1 pt with TP53 clone
for years w/o evolution
(& better Hb...)**

Lecornec & al, Am J Hematol 2026

TABLE 4 | Characteristics of patients with myelodysplastic syndrome or acute myeloid leukemia.

	UPN31	UPN188	UPN196	UPN241
Sex	F	F	M	M
DBAS diagnosis during childhood	Yes	Yes	Yes	Yes
Congenital anomalies	No	Yes	NA	NA
DBAS-associated mutated gene	<i>RPS17</i>	<i>RPS19</i>	NA	No
DBAS status at myeloid malignancy diagnosis	Therapeutic independence	Regular RBC transfusions	Therapeutic independence	Post-HSCT remission
History of solid tumor/type	Yes/CRC	Yes/cholangiosarcoma	No	No
Myeloid malignancy	MDS/AML	MDS	AML	AML
Age at diagnosis (years)	52	48	48	43
Morphology (BM aspirate)	Blast 1%; MLD	Sideroblastic anemia, no excess blast	AML with MLD	AML with MLD
Cytogenetic abnormalities	45, XX, del(5q), -7, add(2q), add(3p), del(20q) [14]/46, XX [6]	45, XX, der(5) t(5; 15) (p13; q12), add(5) (q11), der(6; 21), der(15) t(5;15), add(15) (q12), -17, +mar [11]/46, XX [2]	44-45, XY, der(5), add(5p/q), der(7)/ -7, +11, der(12), der(16), add(17p11), del(18q), -20,+mar	Highly complex monosomal karyotype with abnormalities involving chromosomes 1, 3-5 (del(5q)), 7 (del(7p)), 8-14, 16-18, 21 and 22, with marker, ring, and minute chromosomes
Molecular abnormalities	<i>TP53, RUNX1</i>	NA	<i>WT1</i>	<i>TP53</i>
MDS classification (R-IPPS)	Intermediate risk	High-risk	—	—
Treatment	HSCT up-front	No	Intensive chemotherapy	
HSCT	Yes	No	Yes	Yes
AML/MDS status prior HSCT	Stable	—	CR	CR
Neoplasm status at last FU	AML progression 6 months post-HSCT	Solid tumor progression	AML progression 3 years post-HSCT	AML progression 5 years post-HSCT
Alive at last FU	No	No	No	No
Age at last FU (years)	52	49	52	50

MDS cases (with of w/o leukemic phase)

Cases are difficult to assess within a registry: old cases w/o evidence of clonal evolution, missing data, deceased patients; ...

DBAS patients are not rarely, and wrongly, classified as “MDS”...

To date:

- 2 well-documented cases**
- A few still on investigation**

Precise definitions should be used

Is a systematic screening warranted?

MDS & AML in DBAS patients

Attempt at synthesis

Mean warnings: drop in platelets or unexpected reticulocytes rise: CBC surveillance is warranted. *Clinical benefit associated with sequential myeloid panels analysis (NGS) on blood cells?*

Atypical hematological presentations including unclassifiable leukemias ; MLD frequent

HR karyotype both complex and monosomal with 5q, 7 & 17p anomalies: to be confirmed on more cases

TP53 may be frequently involved*

Work-up for solid cancer is warranted before any intensive treatment

** Simkins & al, JCP Precision Oncology, 2017 (1 case)*

Overall: poor-prognosis presentation

- MDS scoring systems may be not adapted for DBAS cases
- But high frequency of complex and monosomal karyotypes known to be associated with poor post HSCT OS (< 20%)

Lymphoid malignancies in DBAS

Lymphoid malignancies	: Hodgkin lymphoma	: 3
	: NHL	: 2 ⁽¹⁾
	: CLL	: 1 ^{(2), (3)}

1: same pt

2: non severe / not treated

3: higher frequency of MGUS?

DBA: clinical outcomes in adult patients: immunology

Risk for hypo- γ -globulinemia: CVD profile

- Very few clinical problems in my adult patients but...
- Associated with monoclonal proteins?
- 2) Lymphopenia:
 - May be severe
 - In pts on steroids or not

☞ Yearly immunologic evaluation: +++ Ig G, A, M levels

In a pt with low Ig levels:

- ☞ consider specific immunizations: pneumococcal & meningococcal vaccination
- ☞ Lung scan
- ☞ Ig supplementation if clinical infections or occult lung disease (rare)

How to treat adult DBAS patient with anemia ?

1. Transfusions: recommended threshold: 90 to 100 g/dL

- Usually 2 to 3 red cells unit every 3 to 4 weeks
- Take into account QOL
- Less intensive in pts with “high” levels of reticulocytes

2. Glucocorticoids:

- Start prednisone at 2 mg/kg/d (maximal dose 80 mg/j)
- Taper as soon as reticulocytes rise is present (D10-D15)
- Define the minimal efficacious dose

NB: in adult maximal tolerable dose: 10 mg/day

Pretransfusion hemoglobin level and mortality in adults with transfusion-dependent β -thalassemia



Retrospective, 5-centres

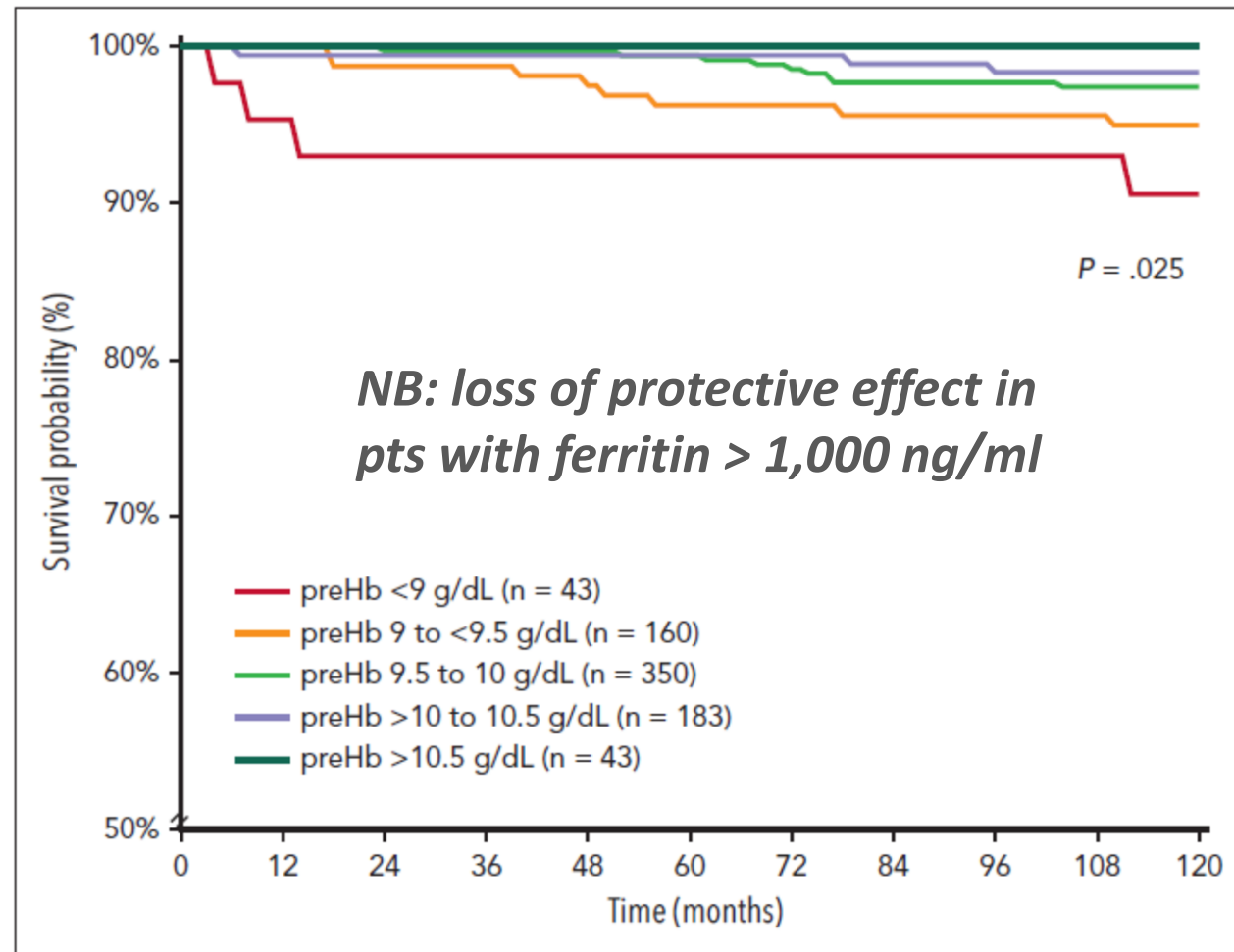
N = 779

NB: Guidelines récents:
9/10, 9/10.5 ou 9.5/10.5

Actual thresholds:

- < 9 N = 43
- 9-9.5 N = 160
- 9.5-10 N = 350 (45%)
- 10-10.5 N = 183 (23%)
- > 10.5 N = 43

Mussalam & al, Blood 2024



DBAS treatment in adults

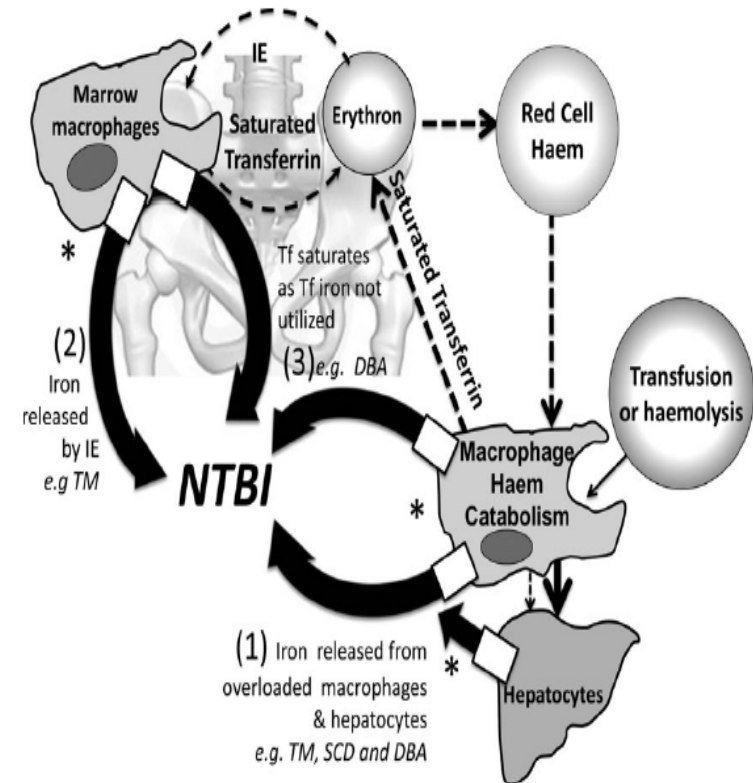
Transfused patients:

Very quick iron loading

Chelation therapy +++

☞ combination of two chelators frequently required

☞ High risk of agranulocytosis with deferiprone (~ 10%)



Porter & al, Br J Haematol 2014

DBAS treatment in adults

Patients on steroids:

Unique disease for the duration of steroid treatment!

Loss of steroid-response not rare with aging: in some pts the choice will be between “too much steroids” (e.g. 15 or 20 mg/d) and transfusions...

Prevention of steroid-associated toxicity +++

☞ regular checking for metabolic syndrome & osteoporosis (sequential osteodensitometry evaluations). Biphosphonates or others (teriparatide) may be needed in selected pts

DBA patients on transfusion

Efficacy of transfusion support:

QOL analysis

Higher blood support requirement with age (> 10 or 10.5 g/dL)

Iron loading FU:

Ferritin levels before each transfusion +++

MRI evaluation: liver & heart: every 12 to 24m

Chelation therapy

Combined therapy should be **systematic**
DFP only in 3rd choice

Follow up for chelators toxicity

+ Hemochromatosis: Regular checks for diabetes, hypoparathyroidy, hypothyroidy, hypogonadism, liver functions, cardiac function,...

Conclusion & take home messages

DBAS is not only a pediatric disease and may be diagnosed in adult patients

DBAS phenotype in adults pts remains in part to be described

DBAS is associated with premature aging of the bone marrow

**DBAS is a cancer-prone disease and clinical guidelines are needed regarding
cancer prevention
detection and treatment**

Genetic counseling is difficult in DBA patients



Merci pour votre attention



thierry.leblanc@aphp.fr



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Patients associations



Reconnue par le Ministère de la Santé

