13/03/2024

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

Presenter: Dr. Giuseppina Aloj

Santobono-Pausilipon Children's Hospital, Naples – Italy.

Expert: Prof. Carmelo Rizzari

MBBM Foundation, ASST Monza, University of Milano-Bicocca, Monza - Italy.

The clinical course of a child with High-Risk Acute Myeloid Leukemia, persistent molecular MRD and SARS-CoV-2 re-infections. What did we learn?

Moderation: Prof. Andishe Attarbaschi

St. Anna Children's Hospital, Medical University of Vienna, Vienna - Austria.

SIOPE YOUNG

St.Anna Kinderkrebs Forschung

Funded by the European Union's EU4Health Programme

COI declaration

- No COI

The patient:

07/04/2022
13 y boy

WBC 235.000/mmc
Hb 5,7 g/dl
PLT 73.000/mmc
Hepatosplenomegaly

Active SARS-CoV-2 infection

Fever (38,3°C)

Mild CRP increase

SpO2 98%, No RDS

Left acute otitis media + otorrhea
gr 2 CTCAE mucositis

Admitted to COVID PICU

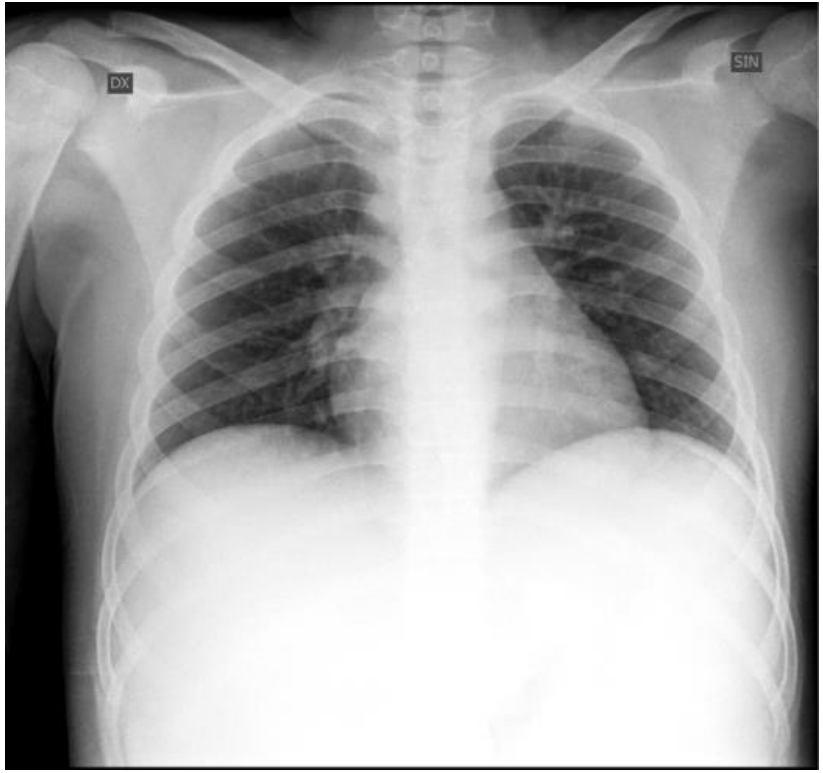
AML FAB M4
FLT3-ITD+ and NPM1+
46XY

CYTOREDUCTION + ANTIBIOTICS (PIPE/TAZO + VANCO)

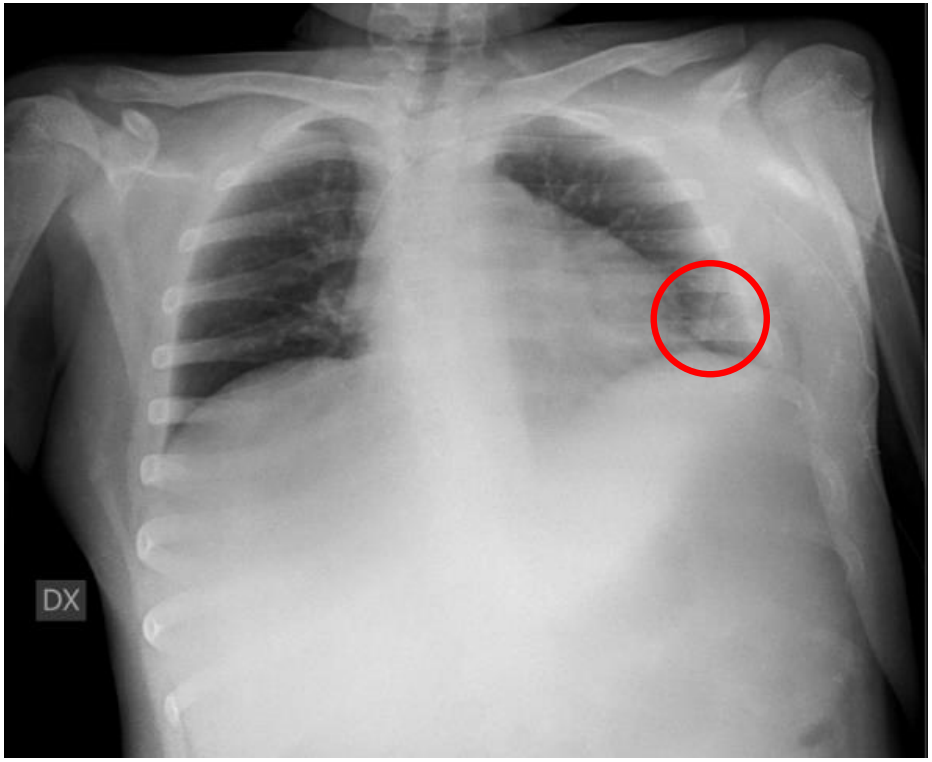
11/04/22
Fever (39°C)
RDS, SpO2 90%
O2 TX 3L/min

LUNG X-RAYS

07/04/2022



12/04/2022



Question 1

- **How would you have managed an AML patient with hyperleukocytosis at onset and a mildly sympthomatic SARS-CoV-2 infection?**

1. Starting the antileukemia + anti SARS-CoV-2 treatment.

2. Treating first the SARS-CoV-2 infection and later the leukemia.

3. Starting the antileukemia treatment without any other anti SARS-CoV-2 treatment.

SARS-CoV-2 in AML pediatric pts: what did we know **in 2022**?

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Immune responses and therapeutic challenges in paediatric patients with new-onset acute myeloid leukaemia and concomitant COVID-19

Patel P.A. et al.

British Journal of Haematology, 2021, **194,** 547–556

2 adolescent new onset AML pts + SARS-CoV-2

Favourable outcome of coronavirus disease 2019 in a 1-year-old girl with acute myeloid leukaemia and severe treatment-induced immunosuppression

Sieni E. et al.

British Journal of Haematology, 2020, **189,** e222–e265

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615.ACUTE MYELOID LEUKEMIA: COMMERCIALLY AVAILABLE THERAPY, EXCLUDING TRANSPLANTATION | NOVEMBER 5, 2020

Successful Outcomes of Children Simultaneously Diagnosed with Acute Myeloid Leukemia and Covid-19: The Role of a Mild Chemotherapeutic Induction Regimen

Mecneide Mendes Lins, MD MMSc,[*,1] Juliana Teixeira Costa, MD,[*,2] Alayde Vieira Wanderley, MD,[*,3] Adriana Seber, MDMS,[4] Cinthya Rocha, MD,[*,5] Luciana Nunes Silva, MD,[*,2] Laudreisa da Costa Pantoja, MD,[*,3] Gustavo Zamperlini, MD,[*,6] Valentino Conter, MD,[*,7] Raul Ribeiro, MD[8]

9 pediatric AML pts (age 5-18); low middle income countries

Received: 13 December 2020 | Revised: 9 February 2021 | Accepted: 14 February 2021
DOI: 10.1111/trf.16361

LETTERS TO THE EDITOR

TRANSFUSION

Planned hematopoietic stem cell transplantation in a 17-month-old patient with high-risk acute myeloid leukemia and persistent SARS-CoV-2 infection

Cuzzubbo D. et al.

What we did for our pt

- Antineoplastic treatment administered during SARS-CoV-2 infection in the PICU for SARS-CoV-2 pts
- **AIEOP-AML 2013-01 Protocol - HR group**
- Administration of Remdesivir together with AML induction
- Readmission to the oncohematology unit one month later, with negative molecular swab test

New patient stratification in the AIEOP LAM 2013 trial

STANDARD RISK (SR) 20-22%	CBFβ anomalies after 1° induction course and MRD < 0.1% at TP1 *–t(8;21)(q22;q22)/[inv(16)(p13q22)/t(16;16)(p13;q22)* Patients with normal karyotype and mutated NPM-1 and MRD < 0.1% at TP1
INTERMEDIATE RISK (IR) 35%	Normal karyotype t(9;11)(p22;q23) without other cytogenetic aberrations t(1;11)(p32;q23) without other cytogenetic aberrations t(11;19) (p13;q23) *t(16;21)(p11;q22)FUS-ERG, t(3;5)(q25;q34)* Other cytogenetic aberrations. M7 with t(1;22), irrespectively of patient's age Other patients not eligible to SR and HR treatment MRD TP1 > 0.1% AND < 1%
HIGH RISK (HR) 40-45%	Cytogenetic aberrations associated with dismal outcome *–Complex karyotype (≥ 3 either numeric or structural aberrations).* *–Monosomal Karyotype (-7, -5)* *–t(9;11)(p22;q23) associated with other cytogenetic aberrations* *–Cytogenetic aberrations involving' 11q23 other than those included in the IR: t(11;17)(q23;q21), t(10;11)(p12;q23), t(4;11)(q21;q23), t(6;11)(q27;q23), t(x;11)* *–Rare cytogenetic aberrations: t(6;9)(p23;q34), t(8-16)(p11;p13), t(9;22)(q34;q11) t(5;11)NUP98/NSD1, t(4;11)MLL/ArgBP2* FLT3-ITD Patients with CN AML and CBFA2T3-GLIS2 fusion transcript FAB M6, M7 without t(1;22), Patients not in CR at the end of the 1° induction course MRD > 1% at TP1 or > 0.1% at TP2 Patients with non-SR criteria and WBC >100.000/mL

Antineoplastic Treatment

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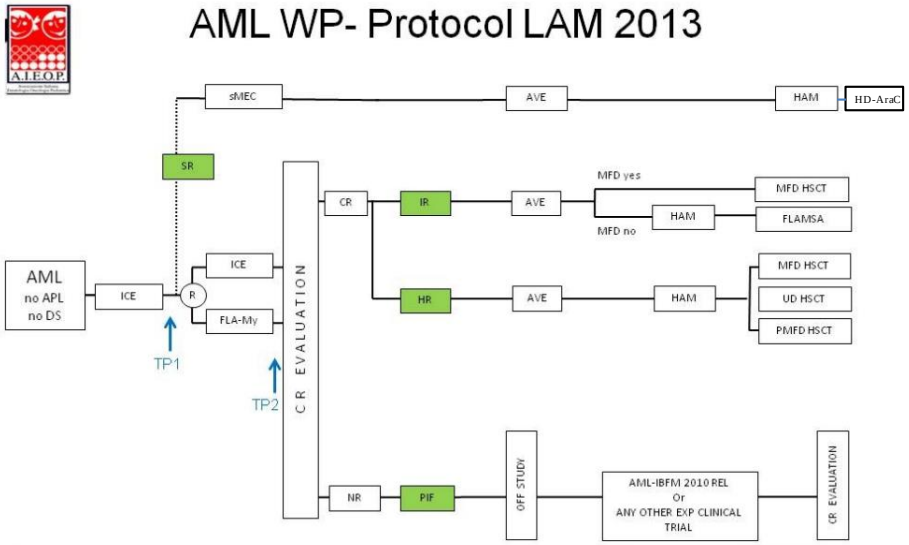
AML WP- Protocol LAM 2013



Legend: APL, Acute Promyelocytic Leukemia; DS, Down Syndrome; SR, Standard Risk; IR, Intermediate Risk; HR, High Risk; CR, Complete Remission; NR, Non Responder; PIF, Primary Induction Failure; TP, Time Point; ICE, 3+5+7 Idarubicin+Citarabine+Etoposide; FLA-My, Fludarabin+Citarabine+Myocet®; sMEC, short MEC (Mitoxantrone, Etoposide, AraC); AVE, Citarabine+Etoposide; HAM, Citarabine+Mitoxantrone; FLAMSA, Fludarabine AraC Amsacrine; HSCT, Hematopoietic Stem Cell Transplantation; MFD, Match Family Donor; UD, Unrelated Donor; PMFD, Partially Match Family Donor.

ICE

GIORNO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	→	21	→	→	28
BM														■		■			■
TIT	■			(*)			(*)			(*)				(*)					
Idarubicina	■	■	■																
Etoposide (ev)	■	■	■	■	■														
Ara-C (ev)	■	■	■	■	■	■	■												

Idarubicina 10 mg/mq/die in SG 5% ev in 4 ore (gg 1,2,3)
Citarabina 200 mg/mq/die in SF ev in ic per 24 ore (gg 1,2,3,4,5,6,7)
Etoposide 100 mg/mq/die in SF ev in 1 ora (gg 1,2,3,4,5)
e
TIT

Fla-My

GIORNO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	→	21	→	→	28
BM														■		■			■
TIT	■			(*)			(*)			(*)				(*)					
Fludarabina (ev)	■	■	■	■	■														
Ara-C (ev)	■	■	■	■	■	■	■												
Myocet®	■		■		■														

Citarabina 2000 mg/mq/die in SF ev per 3 ore (gg 1,2,3,4,5,6,7)
Fludarabina 30 mg/mq/die in SF ev in 30 minuti (gg 1,2,3,4,5)
Myocet® 50 mg/mq/die in SG 5% ev in 2 ore (gg 1,3,5)
e
TIT

MRD assessment

Time points	MFC-MRD	NPM1 RT/RQ PCR	NPM1 RT/RQ PCR	FLT3-ITD RT/RQ PCR
TP1	negative	13%	$6,89 \times 10^{-3}$	$1,67 \times 10^{-4}$
TP2	negative	0,4%	4×10^{-5}	5×10^{-5}

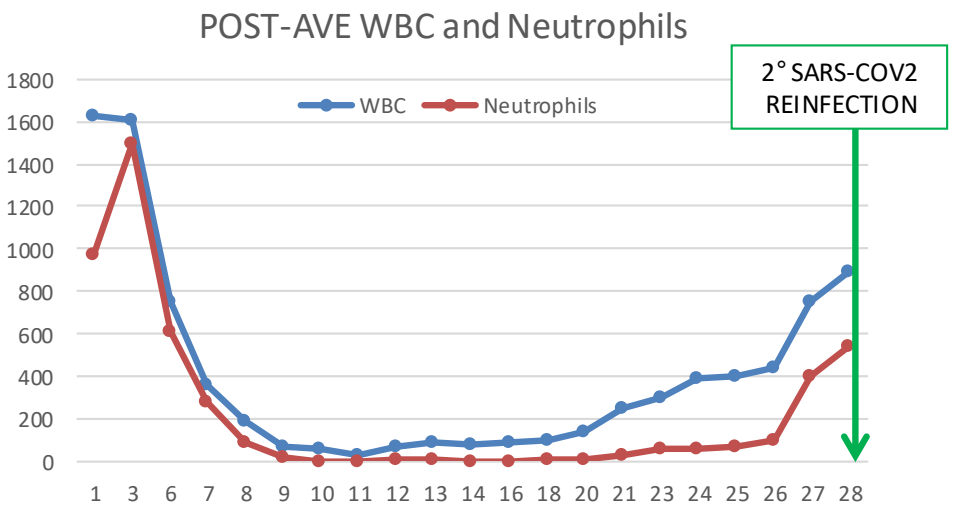
AVE

GIORNO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
BM																					■
TIT						■															
Ara-C (ev)	■	■	■																		
Etoposide (ev)		■	■	■	■																

Ara-C	3 g/mq ogni 12 ore in SG 5% ev in 3 ore (gg 1,2,3)
Etoposide (VEPESID ®)	125 mg/mq/die in SF ev in 1 ora (gg 2,3,4,5)
	Ogni dose di Etoposide va infusa 6 ore prima dell'Ara-C
e	
TIT	

Matched sibling donor available

MILD SARS-CoV-2 REINFECTION (URTI + FEVER)



POST-AVE d+28 WBC 890/mmc; N 540/mmc

Question 2

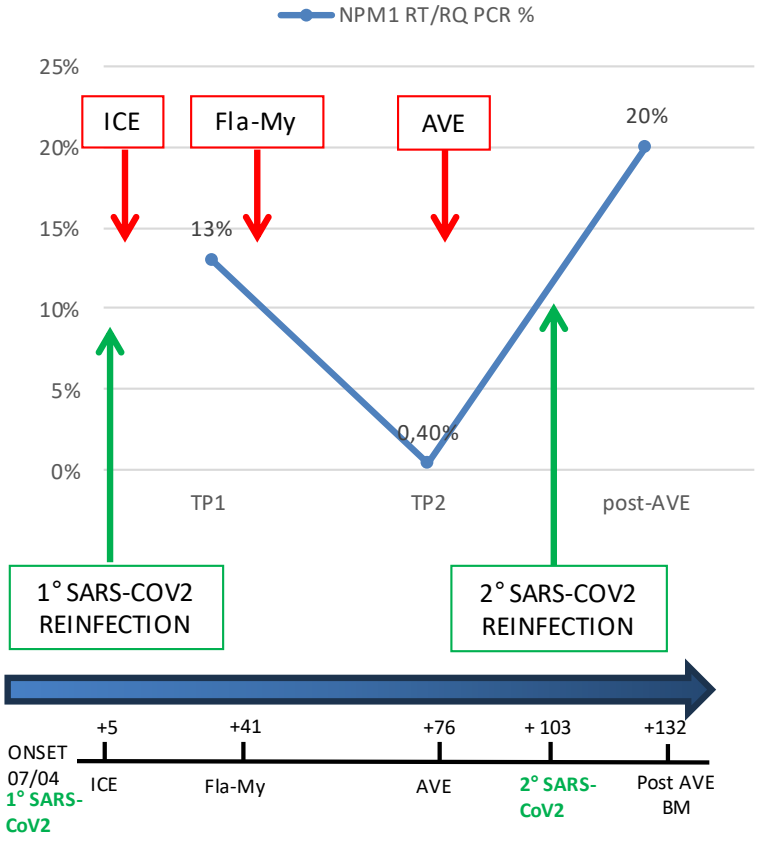
- **At this point, in a mildly sympthomatic SARS-CoV-2 positive AML pt, regenerating from post AVE aplasia, in cytometric and molecular remission, would you have continued with the next block?**

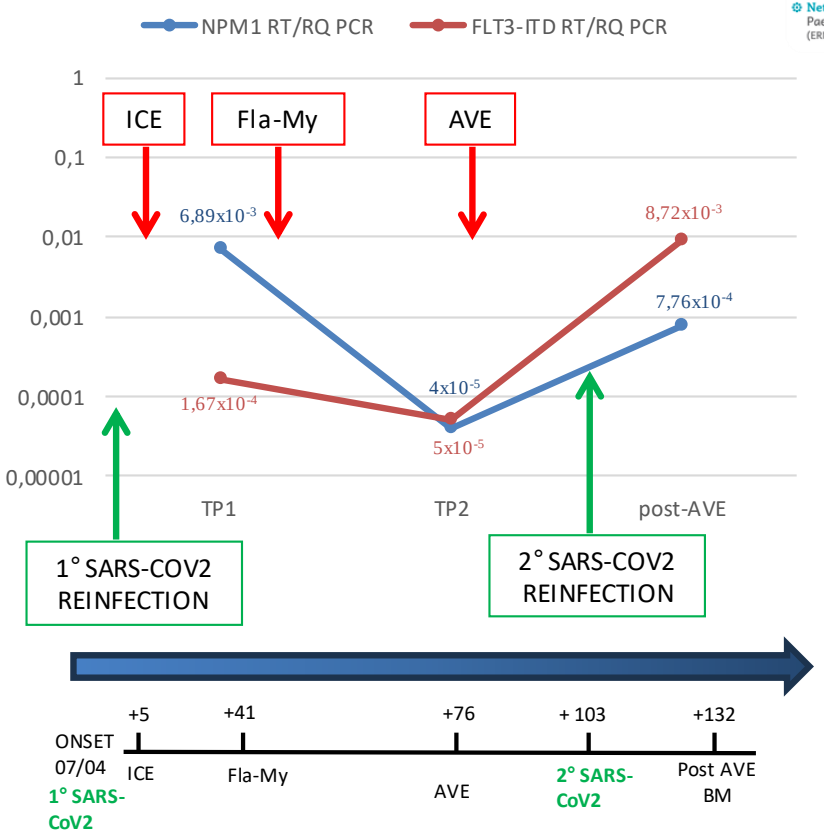
  1. YES, without any anti SARS-CoV-2 treatment.
  2. YES, adding adequate anti SARS-CoV-2 treatment.
  3. NO, waiting for the clinical recovery.
  4. NO, waiting for the negative SARS-CoV-2 molecular swab test.

What we did

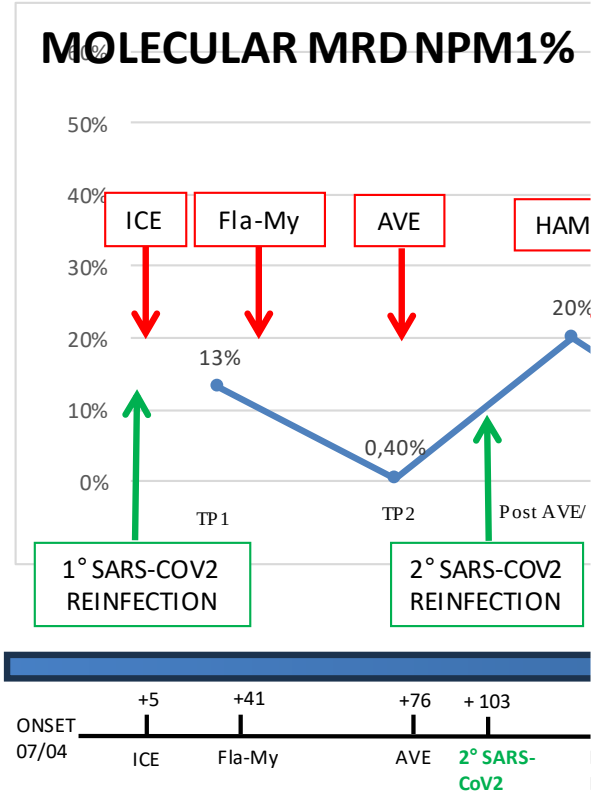
- ADMITTED TO THE INFECTIOUS DISEASE UNIT FOR 8 DAYS.
- MILD COVID19, NO REMDESIVIR.
- CT PAUSED UNTIL NEG MOLECULAR SWAB TEST.
- TOTAL CT ADMINISTRATION DELAY (AVE → HAM) 4 WEEKS.

Molecular MRD: NPM1 and FLT3-ITD RT/RQ PCR





What happened afterwards to molecular MRD:



Was the CT pause a winning choice?

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SARS-CoV-2 Infection in the Pediatric Oncology Population: The Definitive Comprehensive Report of the Infectious Diseases Working Group of AIEOP

Daniele Zama,[1] Andrea Zanaroli,[2] Agnese Corbelli,[3] Andrea Lo Vecchio,[4] Margherita Del Bene,[4] Antonella Colombini,[5] Francesca Compagno,[6] Angelica Barone,[7] Ilaria Fontanili,[7] Maria Rosaria D'Amico,[8] Maria Rosaria Papa,[8] Maria Grazia Petris,[9] Elisabetta Calore,[10,11] Shana Montalto,[12] Linda Meneghello,[13] Letizia Brescia,[14] Rosamaria Mura,[15] Milena La Spina,[16] Paola Muggeo,[17] Simona Rinieri,[18] Cristina Meazza,[19] Katia Perruccio,[20] Monica Cellini,[21] Manuela Spadea,[22,23] Federico Mercolini,[2,24] Valeria Petroni,[25] Raffaella De Santis,[26] Elena Soncini,[27] Massimo Provenzi,[28] Nagua Giurici,[29] Ottavio Ziino,[30] Gloria Tridello,[3] and Simone Cesaro[3]

J Infect Dis NOV 2023
DOI: 10.1093/infdis/jiad496

Table 1. Demographic and Clinical Characteristics of Patients With SARS-CoV-2 Infection

	No. (%) or Median (Range)			
	Asymptomatic	Symptomatic	Total	*P* Value
Patients	196 (43.1)	259 (56.9)	455 (100.0)	
Underlying disease				.6
Acute leukemia, myelodysplasia, lymphoma	114 (58.2)	166 (64.1)	280 (61.5)	
Solid tumor	65 (33.2)	74 (28.6)	139 (30.5)	
Histiocytosis	6 (3.1)	7 (2.7)	13 (2.9)	
Nonmalignant disease	11 (5.6)	11 (4.2)	22 (4.8)	

Table 3. Symptomatic and Asymptomatic Infections During the Years 2020–2022

	Patients, No. (%)			
	2020	2021	2022	*P* Value
Asymptomatic	63 (66.3)	54 (47.0)	79 (32.2)	<.0001
Symptomatic	32 (33.7)	61 (53)	166 (67.8)	
Mild	26 (81.3)	51 (83.6)	158 (95.2)	.004
Nonmild	6 (18.8)	10 (16.4)	8 (4.8)	

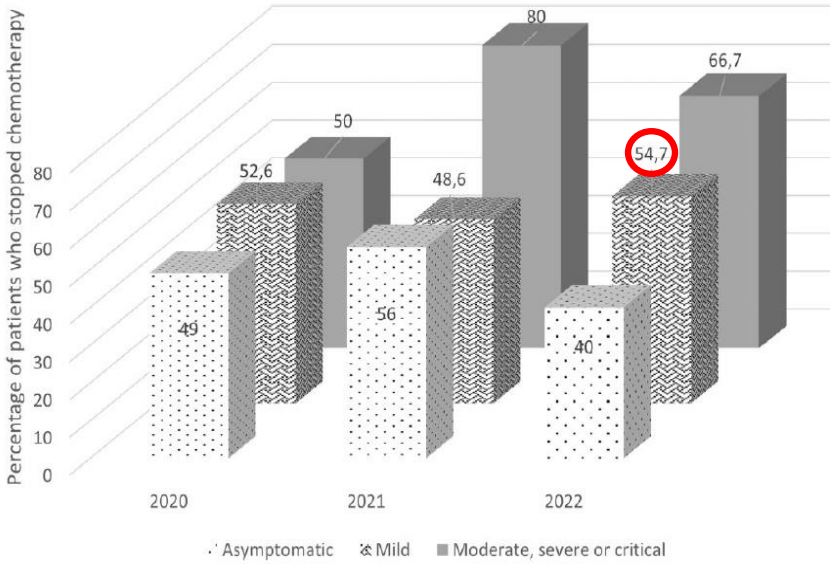

Figure 2. Percentage of pts with an asymptomatic, mild, or nonmild (moderate, severe, or critical) infection who stopped CT, each year of the pandemic.

SARS-CoV-2 in AML pediatric pts: what we know **today**

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European Journal of Pediatrics (2022) 181:1413–1427
https://doi.org/10.1007/s00431-021-04338-y

REVIEW

SARS-CoV-2 in pediatric cancer: a systematic review

Sandy Schlage[1] · Thomas Lehrnbecher[2] · Reinhard Berner[1] · Arne Simon[3] · Nicole Toepfner[1]

- 8 AML pediatric pts
- A mild course of SARS-CoV-2 infection reported in most of the cancer patients (QoE IIT), but a mortality of 6.7%, at least 10 times higher than hospitalized children without comorbidities (QoE IIT).
- Whether and how to proceed with anticancer treatment: a major challenge.
- The risk of cancer progress or relapse has to be weighed against the risk of severe COVID-19.
- Continuation of CT in individual pts seems possible but more data is needed (QoE II_T).

Update of recommendations for the management of COVID-19 [er] in patients with haematological malignancies, haematopoietic cell transplantation and CAR T therapy, from the 2022 European Conference on Infections in Leukaemia (ECIL 9)

Leukemia (2023) 37:1933–1938; https://doi.org/10.1038/s41375-023-01938-5

- Ensure the best possible treatment of the underlying HM disease weighing individual pts risks and benefits
- In HM pts with COVID-19 defer CT after assessment of clinical risk/benefit ratio
- In pts persistently shedding the virus after complete recovery from COVID19, or in pts with asymptomatic SARS-Cov2 infection, defer CT after assessment of clinical risk/benefit ratio

Question 3

- **In your opinion, was the antileukemia treatment discontinuation performed during the 2nd SARS-CoV-2 infection harmful for the patient?**

1. YES
2. NO

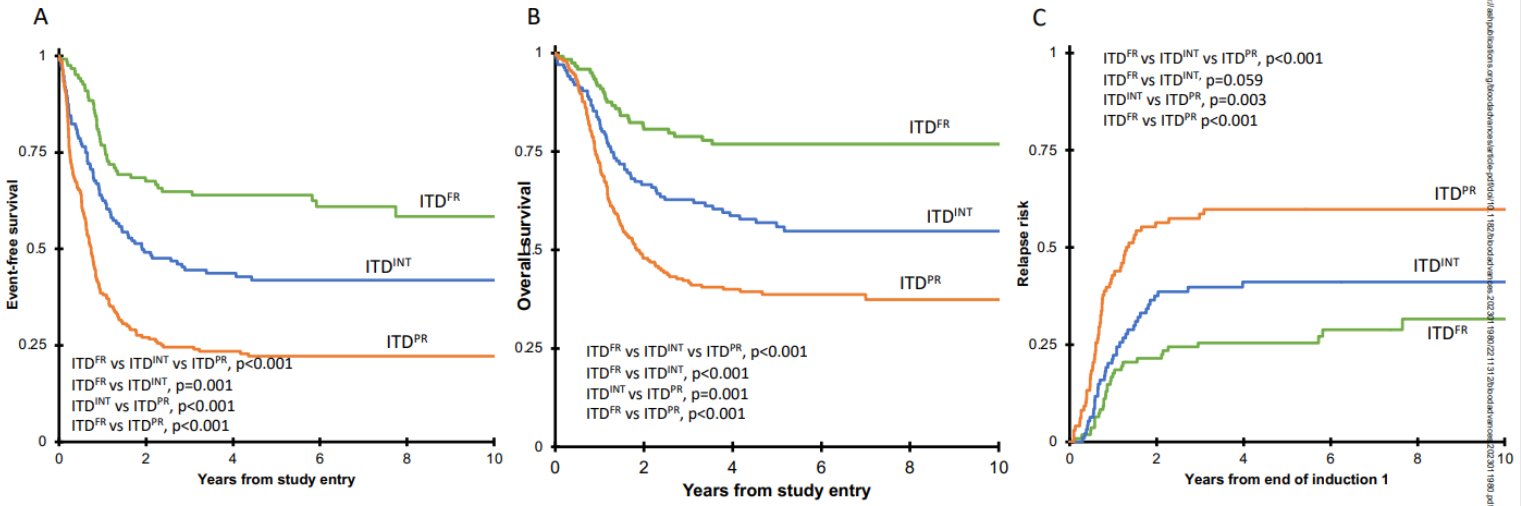
RESEARCH ARTICLE | JANUARY 31, 2024

Prognostic Impact of Co-occurring Mutations in FLT3-ITD Pediatric Acute Myeloid Leukemia

Katherine Tarlock ✉, Robert B Gerbing, Rhonda E. Ries, Jenny L. Smith, Amanda R Leonti, Benjamin J. Huang, Danielle C. Kirkey, Leila Robinson, Jack H. Peplinski, Beverly Lange, Todd M. Cooper, Alan S Gamis, E. Anders Kolb, Richard Aplenc, Jessica A. Pollard, Soheil Meshinchi

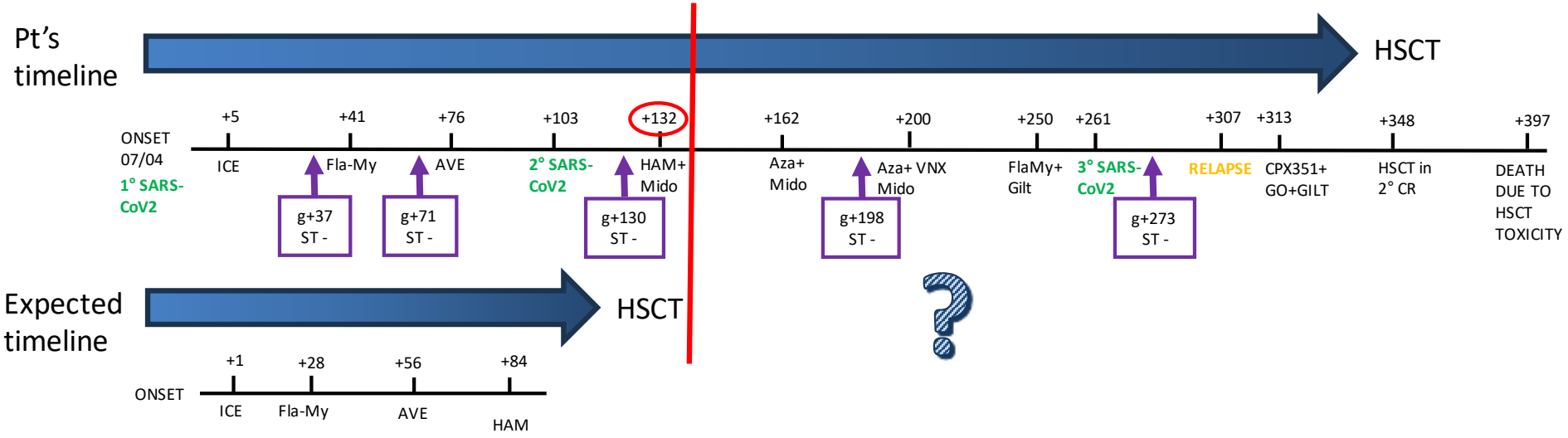
Figure 2

https://doi.org/10.1182/bloodadvances.2023011980



Outcomes for non FLT3-ITD and FLT3-ITDpos pts according to co-occurring mutation risk groups, **favorable (NPM1**, CEBPA, RUNX1-RUNX1T1, CBFB-MYH11), poor (WT1, UBTF, NUP98-NSD1), and intermediate (all other).

Delayed AML treatment and outcome



And what about the reliability of the molecular swab tests?

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DISCUSSION

Funded by the European Union's Health Programme

Take home messages (1)

- Dealing with the therapeutic decisions in CAYA AML pts with SARS-CoV-2 infection was very challenging in the past, when little was known about the real risks related to infected children.

- After the various COVID waves we have learned a lot on the interactions between the SARS-CoV-2 infections/status and childhood cancer: current evidence suggest that **mild/moderate SARS-CoV-2 CAYA AML pts can receive antineoplastic treatment during active infection**, because….

- **…AML has a much worse prognosis than mild/moderate SARS-CoV-2 infections!**

Take home messages (2)

- However, **large and prospective studies about management of SARS-CoV-2 infection in these patients are limited** and mainly consist of retrospectively collected case series.

- From our case and from the clinical experience of recent years we can conclude that **CAYA AML pts with limited or asymptomatic infections can receive moderate or even intensive CT schedule** together with the best available supportive and anti SARS-CoV-2 treatment, ensuring careful monitoring to be shared with infectious disease specialists.

- **Parents and patients have to be carefully informed** about the scientific evidence available in the field and the risks related to any treatment options adopted in such difficult situations.

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THANK YOU

Funded by the European Union's Health Programme

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BACK UP SLIDES

Funded by the European Union's Health Programme

Pre-HSCT Molecular MRD status (rt-qPCR) and relapse risk

biomedicines

MDPI

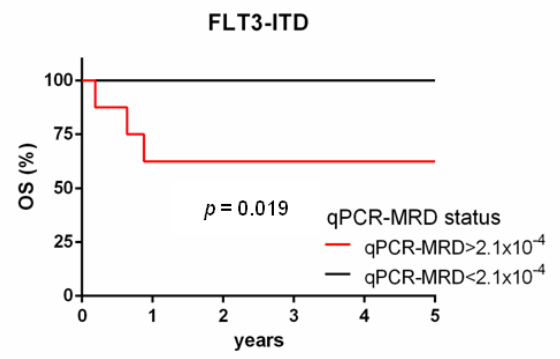
Article

Molecular Measurable Residual Disease Assessment before Hematopoietic Stem Cell Transplantation in Pediatric Acute Myeloid Leukemia Patients: A Retrospective Study by the I-BFM Study Group

Maddalena Benetton [1,†], Pietro Merli [2,†], Christiane Walter [3], Maria Hansen [4], Ambra Da Ros [1], Katia Polato [1], Claudia Tregnago [1], Jonas Abrahamsson [5], Luisa Strocchio [2], Edwin Sonneveld [6], Linda Fogelstrand [7,8], Nils Von Neuhoff [3], Dirk Reinhardt [3], Henrik Hasle [4], Martina Pigazzi [1,*,‡] and Franco Locatelli [2,*,‡]

Biomedicines **2022**, *10*, 1530. https://doi.org/10.3390/biomedicines10071530

112 AML pts; Age 0-18 y



MYELOID NEOPLASIA

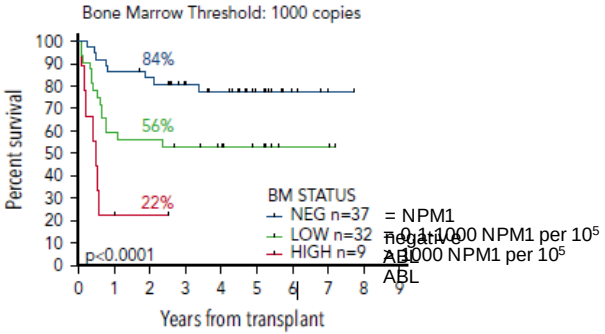
Molecular MRD status and outcome after transplantation in *NPM1*-mutated AML

Richard Dillon,[1-3] Robert Hills,[4] Sylvie Freeman,[5] Nicola Potter,[1,2] Jelena Jovanovic,[1] Adam Ivey,[1] Anju Shankar Kanda,[1] Manohursingh Runglall,[1] Nicola Foot,[2] Mikel Valganon,[2] Asim Khwaja,[6] Jamie Cavenagh,[7] Matthew Smith,[7] Hans Beier Ommen,[8] Ulrik Malthe Overgaard,[9] Mike Dennis,[10] Steven Knapper,[11] Harpreet Kaur,[12] David Taussig,[13] Priyanka Mehta,[14] Kavita Raj,[3] Igor Novitzky-Basso,[15] Emmanouil Nikolousis,[16] Robert Danby,[17] Pramila Krishnamurthy,[18] Kate Hill,[19] Damian Finnegan,[20] Samah Alimam,[1,3] Erin Hurst,[21] Peter Johnson,[22] Anjum Khan,[23] Rahuman Salim,[24] Charles Craddock,[25] Ruth Spearing,[26] Amanda Gilkes,[11] Rosemary Gale,[6] Alan Burnett,[27] Nigel H. Russell,[3,28] and David Grimwade,[1,3] on behalf of the UK National Cancer Research Institute Acute Myeloid Leukaemia Working Group

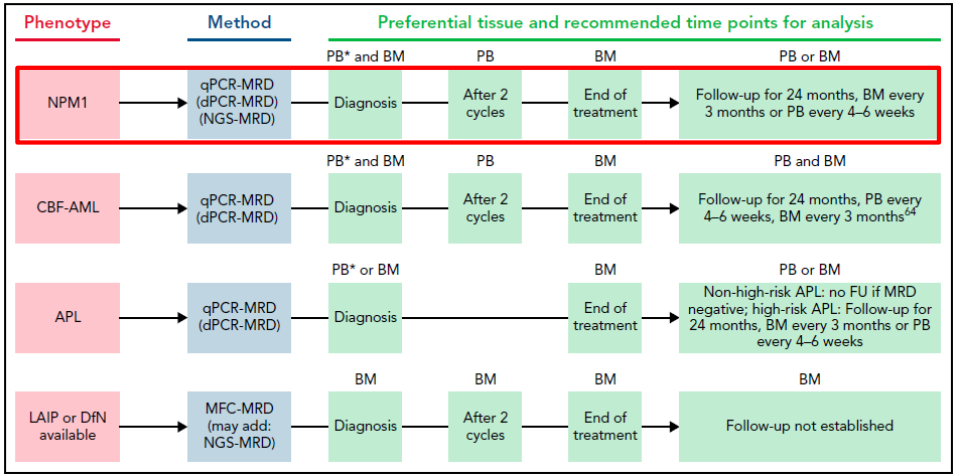
blood® 27 FEBRUARY 2020| VOLUME 135, NUMBER 9

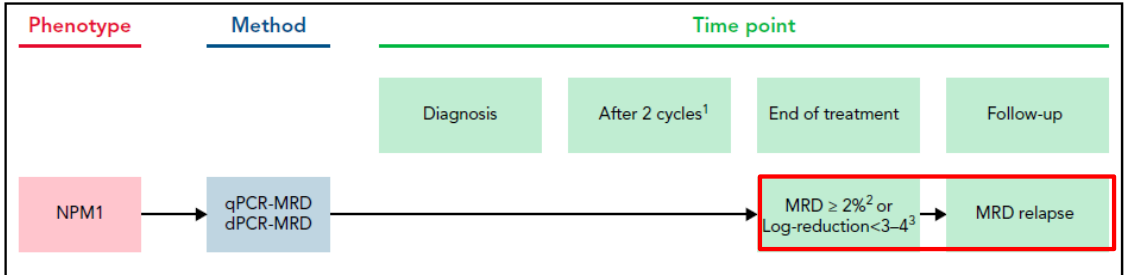
2949 AML pts; Age 16-77 y

NPM1 mutated trascript



Guidelines





2021 Update on MRD in acute myeloid leukemia: a consensus document from the European LeukemiaNet MRD Working Party

Michael Heuser,[1] Sylvie D. Freeman,[2] Gert J. Ossenkoppele,[3] Francesco Buccisano,[4] Christopher S. Hourigan,[5] Lok Lam Ngai,[3] Jesse M. Tettero,[3] Costa Bachas,[3] Constance Baer,[6] Marie-Christine Béné,[7] Veit Bücklein,[8] Anna Czyz,[9] Barbara Denys,[10] Richard Dillon,[11] Michaela Feuring-Buske,[12] Monica L. Guzman,[13] Torsten Haferlach,[6] Lina Han,[14] Julia K. Herzig,[12] Jeffrey L. Jorgensen,[15] Wolfgang Kern,[6] Marina Y. Konopleva,[14] Francis Lacombe,[16] Marta Libura,[17] Agata Majchrzak,[18] Luca Maurillo,[4] Yishai Ofran,[19] Jan Philippe,[10] Adriana Plesa,[20] Claude Preudhomme,[21] Farhad Ravandi,[14] Christophe Roumier,[21] Marion Subklewe,[8] Felicitas Thol,[1] Arjan A. van de Loosdrecht,[3] Bert A. van der Reijden,[22] Adriano Venditti,[4] Agnieszka Wierzbowska,[23] Peter J. M. Valk,[24] Brent L. Wood,[25] Roland B. Walter,[26] Christian Thiede,[27,28] Konstanze Döhner,[12] Gail J. Roboz,[13] and Jacqueline Cloos[3]

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blood® 30 DECEMBER 2021 | VOLUME 138, NUMBER 26

MRD by any methodology during morphological remission after standard CT is a strong prognostic factor for subsequent relapse.

MRD-LL (<2%) is associated with a very low relapse risk in NPM1 mutations when measured at the EOC chemotherapy (GoR A).

Mutations in signaling pathway genes (eg, **FLT3-ITD**, FLT3-TKD, KIT, KRAS, NRAS, and others) most likely represent residual AML when detected, but are often subclonal and have a low negative predictive value. These mutations are best used in combination with additional MRD markers (GoR B).

Refractory AML treatment

A few cooperative international trials for pediatric R/R AML

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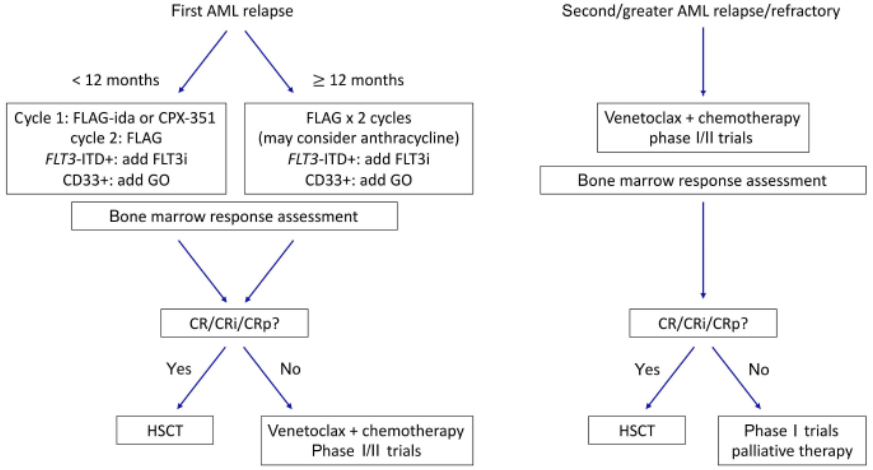
REVIEW ARTICLE

Relapsed pediatric acute myeloid leukaemia: state-of-the-art in 2023

Grace Egan[1] and Sarah K. Tasian[2,3]

https://doi.org/10.3324/haematol.2022.281106



https://doi.org/10.1182/bloodadvances.2023011106.

Venetoclax–based low intensity therapy in molecular failure of *NPM1*-mutated AML

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79 pts
Age 18-81 y

VNX + AZA
VNX + DEC
VNX + LDAC