Leukemia Panel

Dr. Vojdani
Medical Oncologist
& Hematologist

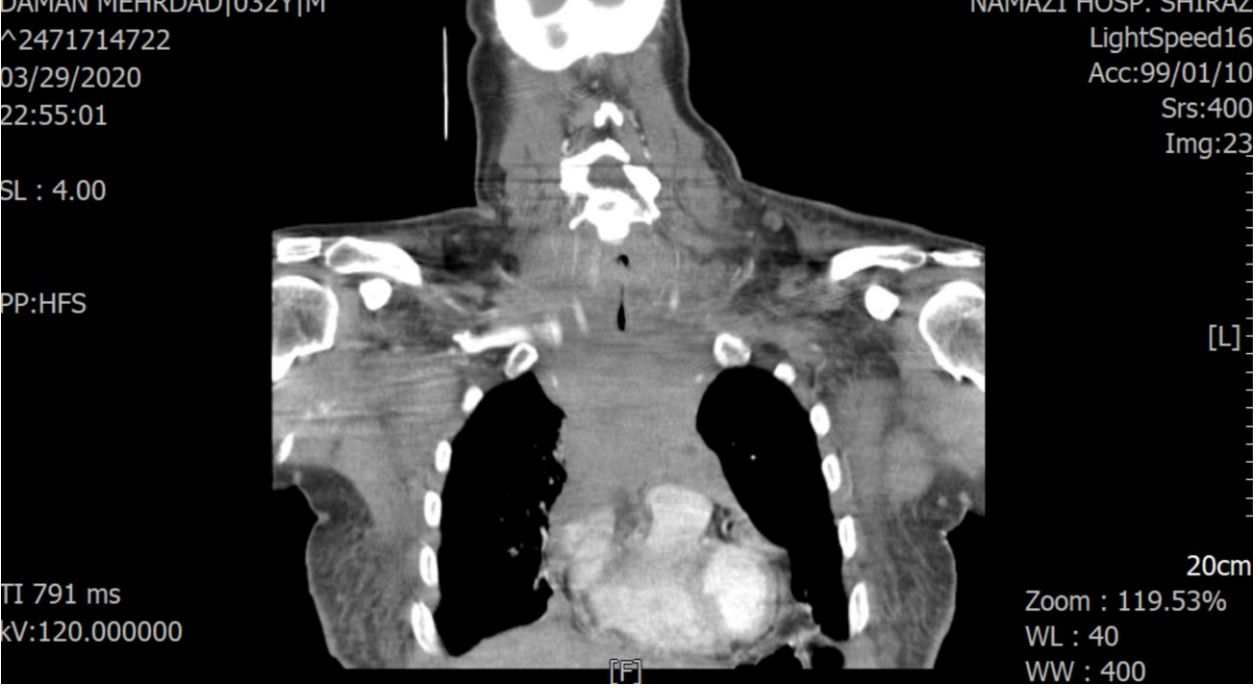
Dr.Ravanbod
medical Oncologist
&Hematologist

Dr. Firouzabadi
Clinical Pharmacist

Dr.Dehghanian
Molecular Pathologist

Case 1

Middle age man with dyspnea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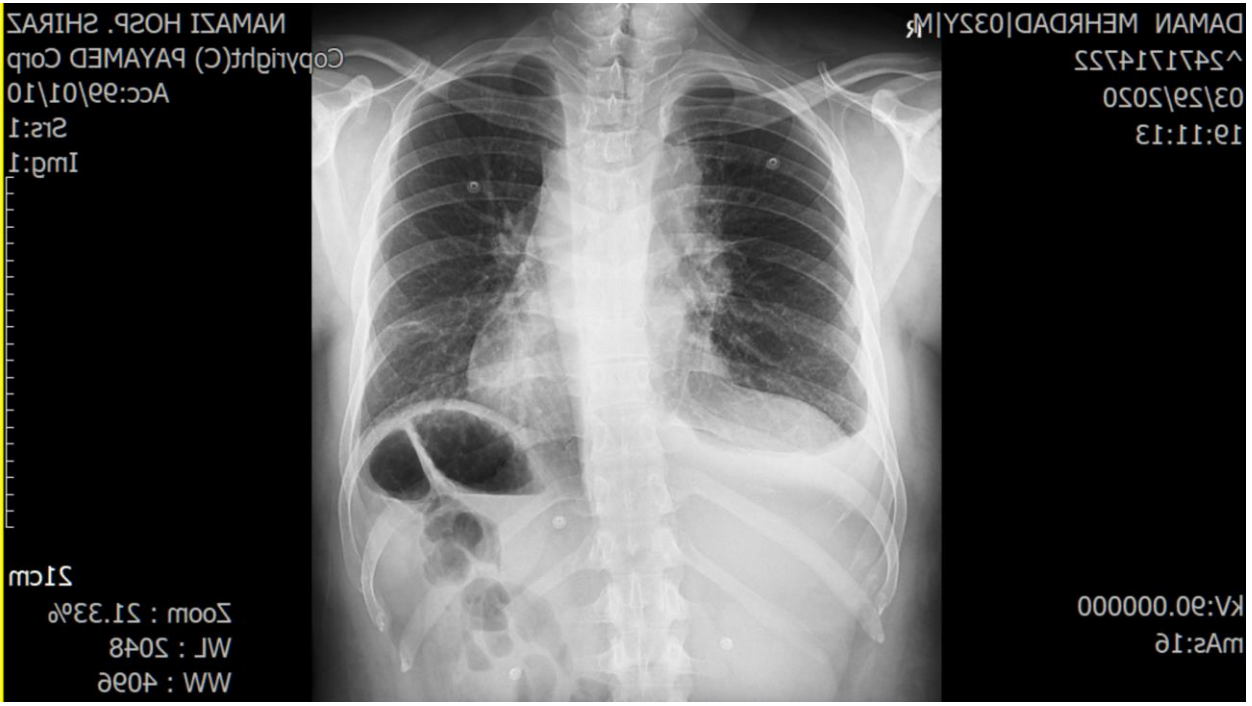
20cm
Zoom : 119.53%
WL : 40
WW : 400
[F]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21cm
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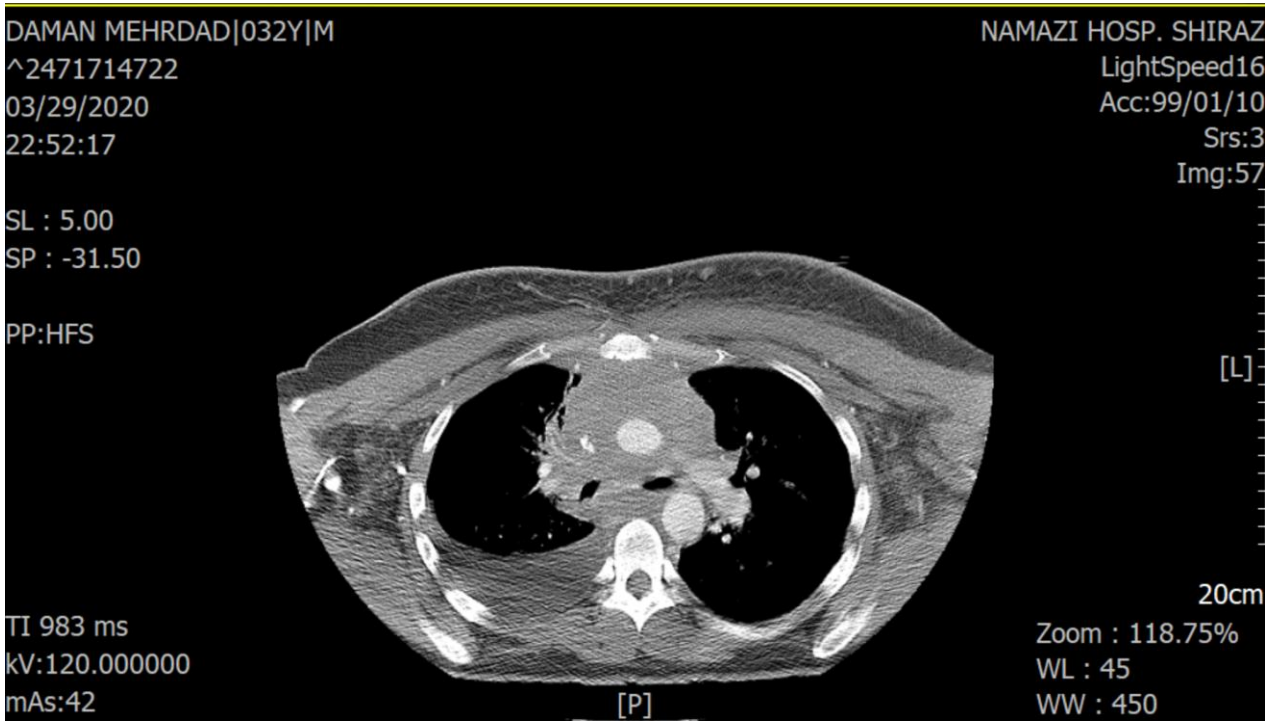
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[L]
20cm
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[P]

- What is your recommendation for more evaluation?

- BMA/B
- PET-SCAN

Chemotherapy

vs

RT

- Standard (7-3)

vs

- High dose Cytarabine

Myeloid sarcoma: current approach and therapeutic options

Batia Avni and Maya Koren-Michowitz

The current recommended treatment regimen in patients presenting with isolated MS or MS presenting concomitantly with AML is conventional AML-type chemotherapeutic protocols

The role of radiotherapy in addition to systemic chemotherapy is not established, although it is often given

Observational Study

Medicine®

OPEN

Intermediate dose cytarabine improves survival and relapse-free rate compared with standard-dose cytarabine as post-remission treatment for acute myeloid leukemia

A retrospection study

Leukemia
https://doi.org/10.1038/s41375-020-01110-3

PERSPECTIVE

Acute myeloid leukemia

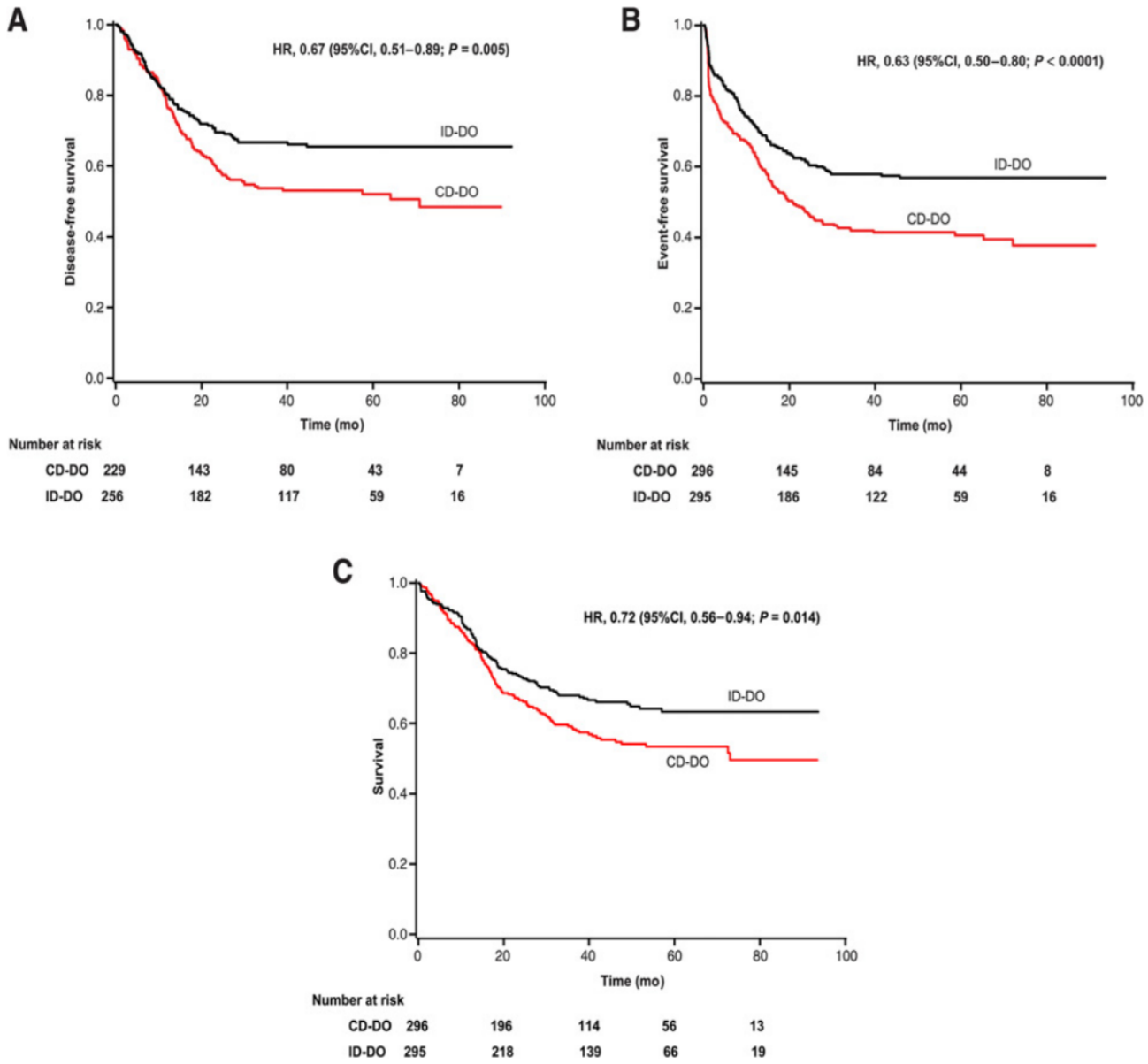
Optimal dosing of cytarabine in induction and post-remission therapy of acute myeloid leukemia

Roland B. Walter[1,2,3,4] · Frederick R. Appelbaum[1,5] · Elihu H. Estey[1,2]

Received: 11 November 2020 / Revised: 20 November 2020 / Accepted: 1 December 2020

Randomized Trial of Intermediate-dose Cytarabine in Induction and Consolidation Therapy in Adults with Acute Myeloid Leukemia

Hui Wei[1,2,3], Ying Wang[2,3], Robert Peter Gale[4], Dong Lin[3], Chunlin Zhou[3], Bingcheng Liu[3], Shaowei Qiu[3], Runxia Gu[3], Yan Li[3], Xingli Zhao[3], Shuning Wei[3], Benfa Gong[3], Kaiqi Liu[3], Xiaoyuan Gong[3], Yuntao Liu[3], Guangji Zhang[3], Zhen Song[2], Yang Wang[5], Wei Li[5], Yingchang Mi[1,2,3], and Jianxiang Wang[1,2,3]



MS development	Extent of involvement	Strategies
Initial	Isolated	Intensive AML chemotherapy with consideration of RT as consolidation
	Concurrent MS and marrow	Intensive AML chemotherapy with consideration of HCT; RT if MS persists after induction chemotherapy
Relapse	**Isolated**	
	After chemotherapy	Reinduction AML chemotherapy with consideration of HCT
	After transplant	Donor lymphocyte infusion, tapering of immunosuppression, RT, and/or clinical trial
	MS and marrow	
	After chemotherapy	Reinduction AML chemotherapy with consideration of HCT, RT, and/or clinical trial
LC	**Marrow status**	**Strategies**
	Negative	Intensive AML chemotherapy
	AML	Intensive AML chemotherapy with consideration of HCT; TSEB after chemotherapy for persistent LC if marrow negative

In a group of 19 MS patients (17 patients with concurrent AML at presentation) we found that the median time to death was the same in patients receiving radiotherapy in addition to chemotherapy and those not receiving radiotherapy.

Similarly, Lan and colleagues found **no effect on survival** in MS patients (isolated or following the diagnosis of AML) treated with radiotherapy in addition to chemotherapy compared to chemotherapy alone.

Radiotherapy **may not be needed** as an adjunct to chemotherapy

Radiotherapy should be considered in isolated MS

- **Inadequate** response to chemotherapeutic regimen
- **In recurrence** following bone marrow transplantation
- **When** rapid symptom relief is needed.

Using a regimen of 24 Gy in 12 fractions can be offered to most MS patients with outstanding disease control and negligible morbidities

Role of Cytogenetic In myeloid Sarcoma?

Cytogenetic analysis conducted with bone marrow and peripheral blood blasts in myeloid sarcoma patients has demonstrated cytogenetic abnormalities in more than 50% of instances

However, studies by Pileri et al. showed the relative rarity of t(8,21) in adult myeloid sarcoma patients.
Instead, trisomy 8, monosomy 7 and MLL rearrangements constitute the majority of the cases

Other chromosomal aberrations including monosomy 5, 7 or 8 were reported in isolated cases

They reported full concordance between FISH and conventional cytogenetics in
71% of patients with available data.
This may suggest that conventional cytogenetic studies on bone marrow or peripheral blood and FISH studies on sarcoma cells are complementary and in a clinical setting, they should both be performed

What is your Concept about decision making in this case?

- Risk Oriented

VS

- Response Oriented

Does the presence of EM involvement confer a worse prognosis than AML without EM disease?

Although the presence of EM disease may be associated with a **poor prognosis and shorter survival**,
5-year survival rates for patients with MS range between 20% and 30%, which appear similar to AML in general

Although the presence of translocation t(8;21) is associated with a relatively good prognosis when treated with standard induction and intensive consolidation chemotherapy, it remains unclear whether this **favorable prognosis remains in the presence of EM disease because there are conflicting report**

Byrd et al analyzed 84 AML patients with t(8;21) and reported that those with EM disease **had significantly worse survival,** which in part could have been the result of including a high proportion of patients with spinal or meningeal involvement

Until we have more definitive data:
we consider MS an additional poor prognostic factor in the overall evaluation of AML.

We consider LC a marker of **aggressive disease** that can be difficult to control and patients prone to EM relapses

Data on the prognostic significance of myeloid sarcoma are limited. Although the presence of extramedullary leukemia may be associated with a poor prognosis and shorter survival, 5-year survival rates for patients with myeloid sarcoma range between 20% and 30%, which appear similar to AML in general

Although the presence of translocation t(8;21) is associated with a relatively good prognosis when treated with standard induction and intensive consolidation chemotherapy, it **remains unclear** whether this favorable prognosis remains in the presence of **extramedullary leukemia** because there are conflicting reports

Until we have more definitive data, experts consider myeloid sarcoma an additional poor prognostic factor in the overall evaluation of AML.

Do you recommend imaging for evaluation of response?

18F-FDG PET/CT does have some restrictions.
Several reports have shown that 18F-FDG PET/CT is not sensitive enough to pick up extramedullary infiltration in the **soft tissues such as skin meninges and mucus membranes**

For consolidation?

- HiDAC

Vs

- BMT

Randomized Trial of Intermediate-dose Cytarabine in Induction and Consolidation Therapy in Adults with Acute Myeloid Leukemia

Hui Wei[1,2,3], Ying Wang[2,3], Robert Peter Gale[4], Dong Lin[3], Chunlin Zhou[3], Bingcheng Liu[3], Shaowei Qiu[3], Runxia Gu[3], Yan Li[3], Xingli Zhao[3], Shuning Wei[3], Benfa Gong[3], Kaiqi Liu[3], Xiaoyuan Gong[3], Yuntao Liu[3], Guangji Zhang[3], Zhen Song[2], Yang Wang[5], Wei Li[5], Yingchang Mi[1,2,3], and Jianxiang Wang[1,2,3]

The post remission chemotherapy has not been adequately studied in isolated MS; and in particular, the role of HCT is not clear

There is no evidence that this combined approach is superior to aggressive chemotherapy alone

Bone Marrow Transplantation

While there are no prospective trials evaluating the role of bone marrow transplantation in isolated MS, **some retrospective** studies show good results and even encourage considering allogenic bone marrow transplantation after the patients' first induction of remission

However, extramedullary infiltration by acute leukemia strongly implicates the presence of an alternative homing signal that enables the blast cells to re-localize to these secondary sites

The authors reported that a major factor for the migration of AML cells into non-myeloid regions is the interactions between matrix metalloproteinase (MMP) – 9 and leukocyte β2 integrin along with some unidentified proteins

Stefanidakis et al. termed the complex, ‘invadosome”. The observations that highly invasive AML cell lines express high level of MMP-2 and tissue inhibitor of metalloproteinase 2 (TIMP2) further support the conclusion of Stefanidakis and colleagues.

In a recent study, Zhu et al. has reported a correlation between high expression of enhancer of Zeste 2 (EZH2), the catalytic subunit of poly comb repressor complex 2 (PRC2), and extramedullary infiltration of AML. The authors have indicated that increased expression of EZH2 attenuates the expression of TIMPs, which result in the upregulation of MMPs. The uninhibited MMPs ultimately degrades the extracellular matrix (ECM) and thus aid in the escape of the blast cells in the extramedullary space 43).

Case 2

52 years old with pancytopenia
BMA,BMB

Immunohistochemistry Report

CD123	Negative
CD3	Negative
CD4	Negative
CD56	Positive in 30% of cells
CD68	Negative
Glycophorin A	Positive in erythroid series
MPO	Positive in 30% of cells
Pax-5	Negative
Perforin	Negative
TDT	Positive diffusely

Mixed phenotype acute leukemia (MPAL)

- MPALs express markers of one or more lineages to a significant degree

- MPALs may be:
  - Bilineal: two separate blast populations each of a different lineage
  - Biphenotypic: one blast population expressing markers of two different lineages
  - Rare cases showing trilineage differentiation have been described

- Specific cytogenetic abnormalities may be associated with MPAL
  - t(9;22)(q34;q11.2);BCR-ABL1
  - t(v;11q23);MLL rearranged

- Flow cytometry is integral in the diagnosis of MPAL

Challenge in diagnosis of mixed phenotype

Lineage Assignment Criteria
Myeloid Lineage
MPO+ (Flow cytometry, immunohistochemistry, or cytochemistry) or Monocytic differentiation (at least two of the following: nonspecific esterase cytochemistry, CD11c, CD14, CD64, lysozyme)
T-Lymphoid Lineage
Strong * cytoplasmic CD3 (with antibodies to CD3 ε chain) or Surface CD3
B-Lymphoid Lineage
Strong * CD19 with at least 1 of the following strongly expressed: CD79a, cytoplasmic CD22, or CD10 or Weak CD19 with at least 2 of the following strongly expressed: CD79a, cytoplasmic CD22, or CD10

Table 2. 2008/2016 WHO criteria for the classification of mixed-phenotype acute leukemia (MPAL).

Lineage	Markers
Myeloid	Myeloperoxidase or Monocytic differentiation - at least two of the following markers: NSE, CD11c, CD14, CD64, lysozyme
T-cell	Cytoplasmic CD3 or Surface CD3
B-cell	Strong CD19 expression AND strong expression of at least one of the following markers: CD79a, cCD22, CD10 or Weak CD19 expression AND strong expression of at least two of the following markers: CD79a, cCD22, CD10

Table 2. WHO 2016 criteria for acute leukemia of ambiguous lineage.

Acute Undifferentiated Leukemia
Mixed-phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); BCR-ABL1
MPAL with t(v;11q23.3); KMT2A rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS

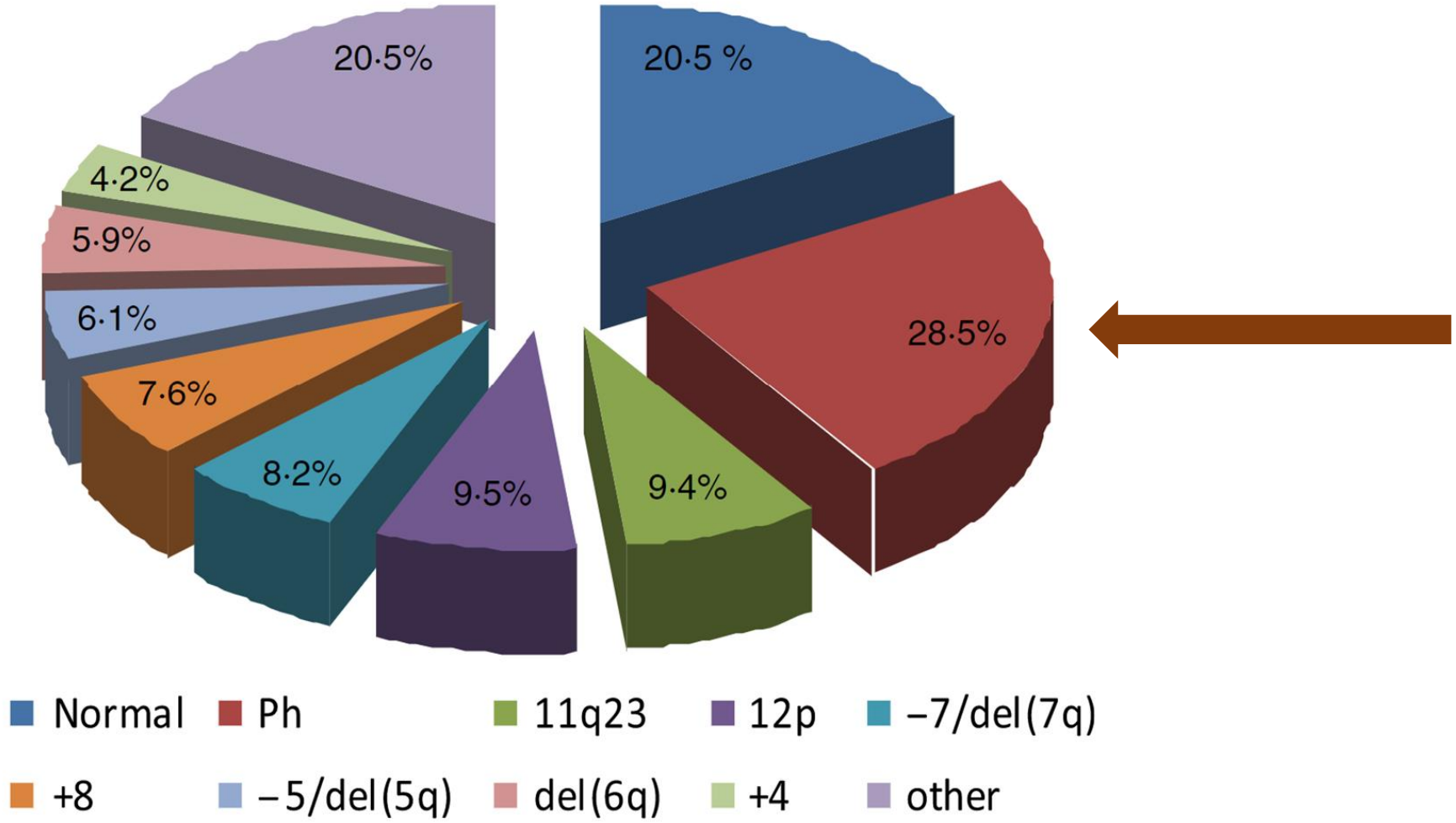
Table 2. Diagnostic criteria for mixed-phenotype acute leukemia according to the WHO revision of classification 2016 (ref.[5]).

Lineage	Markers
Myeloid	myeloperoxidase or monocytic differentiation (at least two of the following markers: NSE, CD11c, CD14, CD64 or lysozyme)
T-lymphoid	cytoplasmic or surface CD3
B-lymphoid	strong expression of CD19 and at least one of the following markers: CD79a, cytoplasmic CD22, CD10; or weak expression of CD19 and at least two of the following markers: CD79a, cytoplasmic CD22, CD10

Table 3. Categories of MPAL according to the 2008 WHO classification[4].

Category	Definition
MPAL with t(9;22) (q34;q11.2); *BCR-ABL1*	acute leukemia meeting the criteria for MPAL, with blasts carrying translocation (9;22) or *BCR-ABL1* rearrangement
MPAL with t(v;11q23); *MLL* rearrangement	acute leukemia meeting the criteria for MPAL, with blasts carrying translocation involving the *MLL* gene
MPAL, B/myeloid, NOS	acute leukemia meeting the criteria for B-lymphoid and myeloid lineages of MPAL, with blasts not carrying genetic abnormalities involving *BCR-ABL1* or *MLL*
MPAL, T/myeloid, NOS	acute leukemia meeting the criteria for T-lymphoid and myeloid lineages of MPAL, with blasts not carrying genetic abnormalities involving *BCR-ABL1* or *MLL*
MPAL, NOS	acute leukemia meeting the criteria for B- and T-lymphoid lineages or trilineage MPAL
Other entities classified as MPAL	NK-cell lymphoblastic leukemia/lymphoma acute bilineal leukemia

What is your recommendation about cytogenetic study in this case?



ALL like regimen
vs
AML like regimen

Why??

- Less intensive chemotherapy +TKI

vs

- intensive chemotherapy + TKI

Acute lymphoblastic leukemia–like treatment regimen provides better response in mixed phenotype acute leukemia: a comparative study between adults and pediatric MPAL patients

Eman O. Rasekh[1] · Randa Osman[1] · Dalia Ibraheem[2] · Youssef Madney[3] · Enas Radwan[1] · Abdallah Gameel[1] · Ahmed Abdelhafiz[1] · Azza Kamel[1] · Sally Elfishawi[1]

Received: 21 July 2020 / Accepted: 17 November 2020

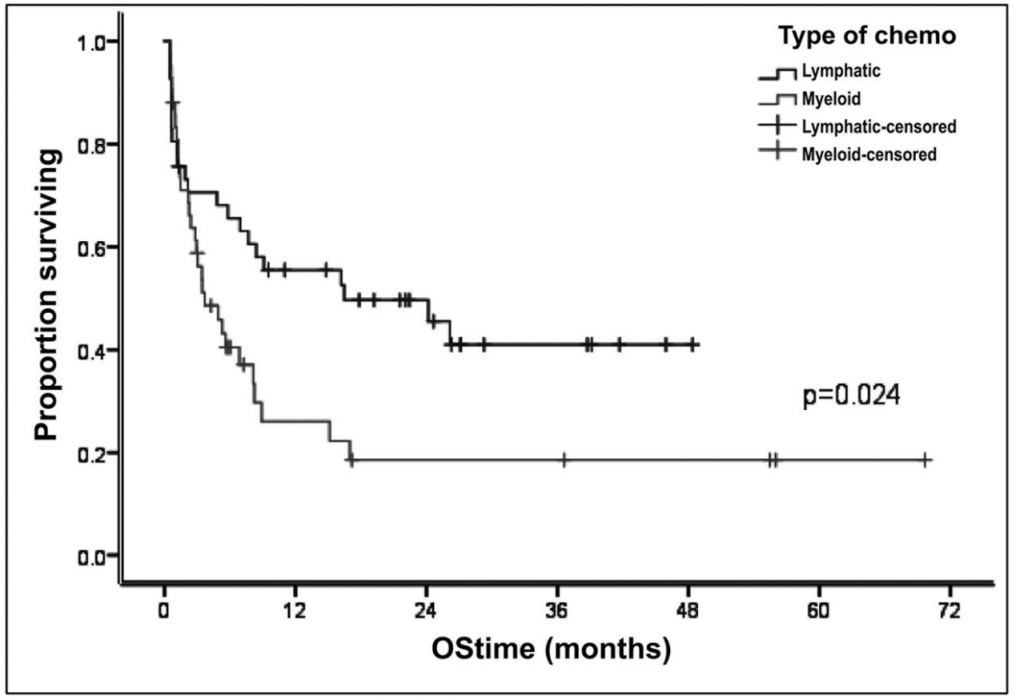
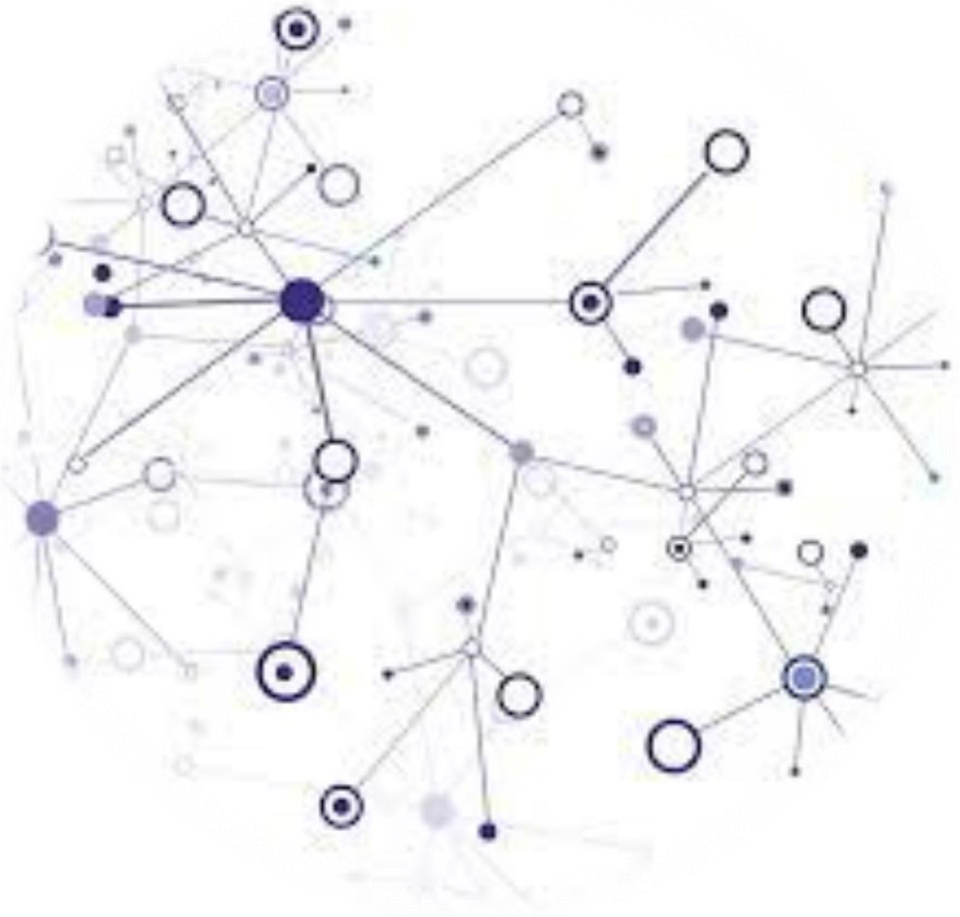


Fig. 3 Overall survival of 102 mixed phenotype acute leukemia patients treated with lymphatic regimen vs. myeloid treatment ($p = 0.024$)

- How we can evaluate MRD in such patients?

MRD oriented
vs
Risk oriented

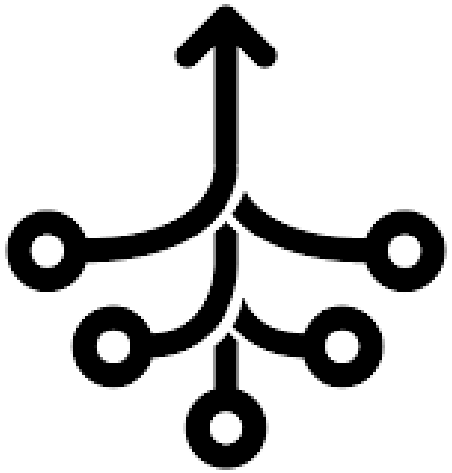


Consolidation?

BMT

Vs

ALL like maintenance treatment



ORIGINAL ARTICLE

Allogeneic hematopoietic stem cell transplantation for adult patients with mixed phenotype acute leukemia: results of a matched-pair analysis

Hiroaki Shimizu[1], Takayuki Saitoh[1], Shinichiro Machida[2], Shinichi Kako[3], Noriko Doki[4], Takehiko Mori[5], Toru Sakura[6], Yoshinobu Kanda[3], Heiwa Kanamori[7], Shuichi Miyawaki[8], Shinichiro Okamoto[5] for Kanto Study Group for Cell Therapy (KSGCT)

Original Article

Mixed-Phenotype Acute Leukemia: A Cohort and Consensus Research Strategy From the Children's Oncology Group Acute Leukemia of Ambiguous Lineage Task Force

Mixed phenotype acute leukemia: outcomes with allogeneic stem cell transplantation. A retrospective study from the Acute Leukemia Working Party of the EBMT

Reinhold Munker,[1] Myriam Labopin,[2] Jordi Esteve,[3] Christoph Schmid,[4] Mohamad Mohty[2] and Arnon Nagler[5,6]

Myeloablative conditioning using **total body irradiation** correlated with a better leukemia-free survival.
Our study suggests that mixed phenotype acute leukemia is potentially sensitive to graft-versus-leukemia and thus can benefit from allogeneic hematopoietic stem cell transplantation with a potential for cure

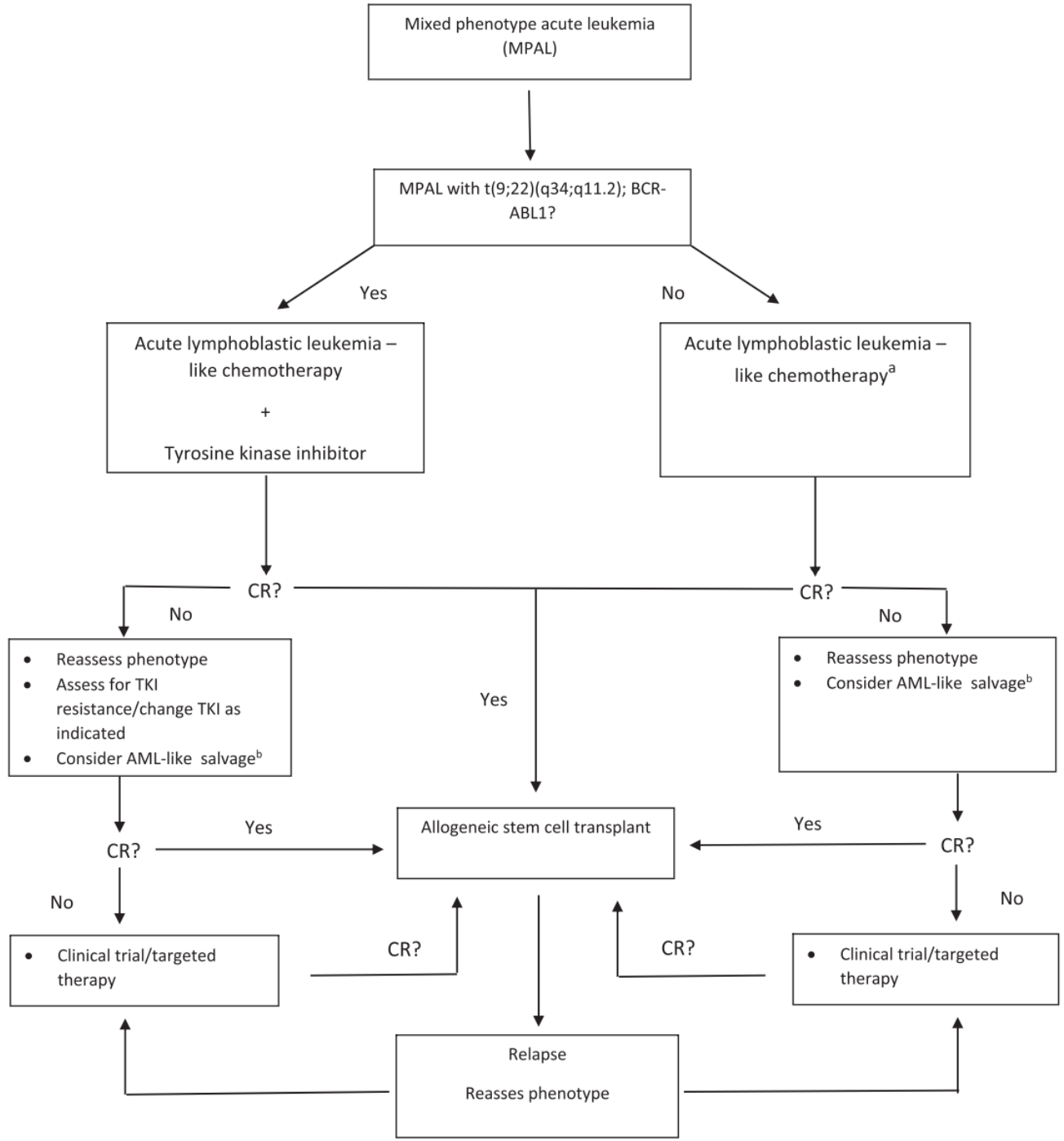
Best Option in R/R case?

AML like regimen

FlAG/Ida

Ventoclax+ Azacytidine

Other TKI


Mixed phenotype acute leukemia (MPAL)
MPAL with t(9;22)(q34;q11.2); BCR-ABL1?
Yes
No
Acute lymphoblastic leukemia – like chemotherapy + Tyrosine kinase inhibitor
Acute lymphoblastic leukemia – like chemotherapy[a]
CR?
No
Yes
CR?
No
Reassess phenotype
Assess for TKI resistance/change TKI as indicated
Consider AML-like salvage[b]
Yes
Reassess phenotype
Consider AML-like salvage[b]
CR?
Yes
Allogeneic stem cell transplant
Yes
CR?
No
No
Clinical trial/targeted therapy
CR?
CR?
Clinical trial/targeted therapy
Relapse
Reasses phenotype

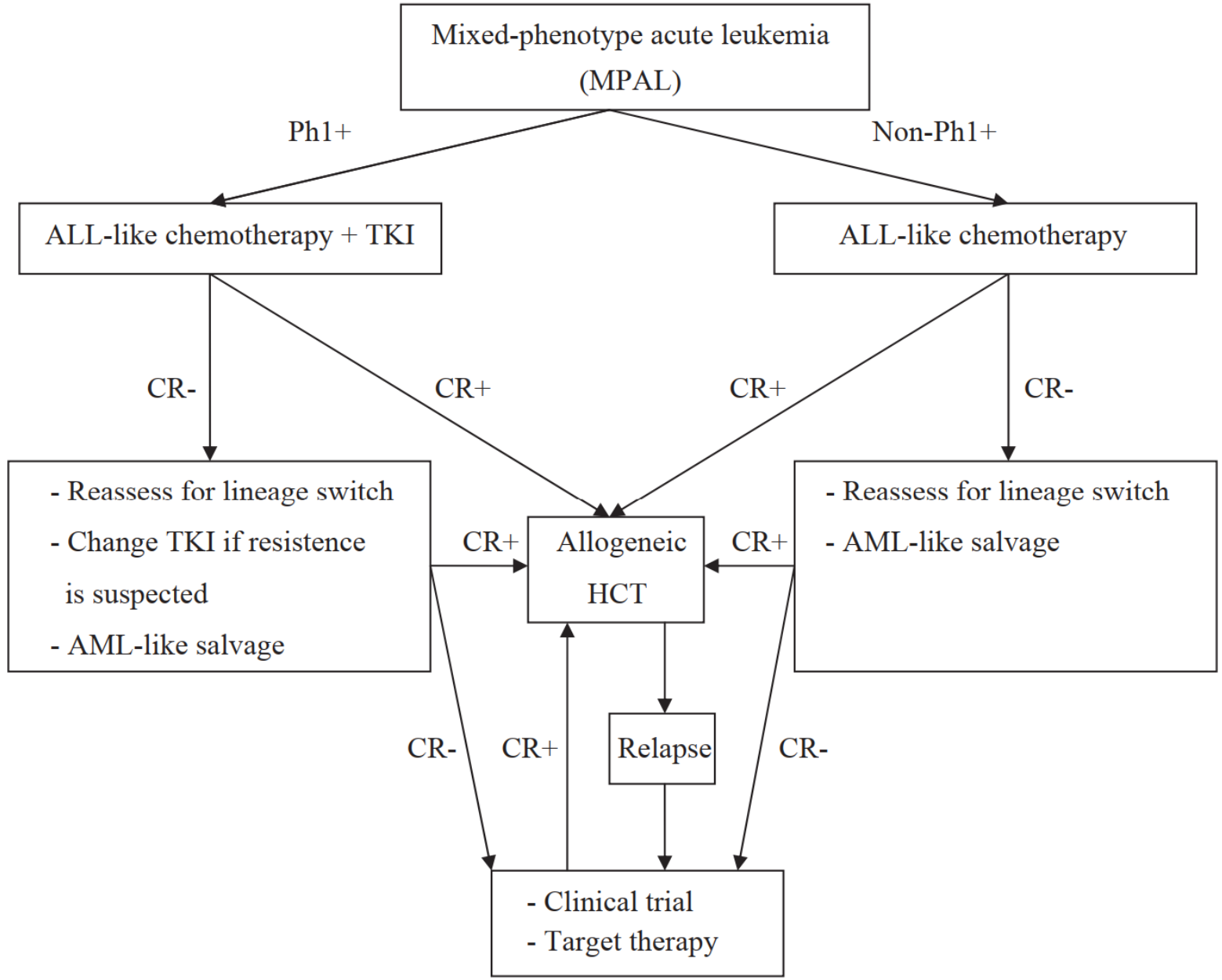

Mixed-phenotype acute leukemia (MPAL)
Ph1+
Non-Ph1+
ALL-like chemotherapy + TKI
ALL-like chemotherapy
CR-
CR+
CR+
CR-
- Reassess for lineage switch
- Change TKI if resistence is suspected
- AML-like salvage
CR+
Allogeneic HCT
CR+
- Reassess for lineage switch
- AML-like salvage
CR-
CR+
Relapse
CR-
- Clinical trial
- Target therapy

Table 1. Potential biological-driven interventions for mixed phenotype acute leukemia[a]

Target/modality	Implications/examples	Reference
MRD-directed interventions	Risk-adapted approach based on MRD according to protocol-derived time points. e.g. Blinatumomab in CD19+ postchemotherapy MRD.	[37,38,39▪]
Tyrosine-kinase inhibitors	For BCR-ABL1-driven MPAL For MPAL with Ph-like expression (specific TKi based on specific activating lesion)	[43] [63,64]
FLT3 inhibition	For *FLT3* mutated (enriched for T/myeloid) For FLT3 pathway overexpressors: *ZNF384*-rearranged B/myeloid MPAL *MLL*-rearranged MPAL	[17▪▪,18] [17▪▪]
T-cell-engaging therapies	Blinatumomab and CD19 CAR-T cells for CD19-expressing relapsed MPAL based on extrapolation from BCP-ALL. Potential for lineage switch	[55–60]
Immunophenotype-driven therapy	Monoclonal antibodies (naked, conjugated) based on MPAL phenotype (CD19, CD20, CD22, CD38, CD123, etc.) in extrapolation from AML and ALL	
Mutation-driven therapy	For targetable mutations and pathways in extrapolation from AML and ALL	
Inhibiting key survival pathways	BCL2 inhibition based on efficacy in other related stem-cell leukemias, such as ETP-ALL Hedgehog pathway inhibitors in extrapolation from AML	[17▪▪,65,66] [67]
MLL-directed therapy	DOT1L, menin, or bromodomain inhibitors	[44]


Photo: Amir Tavakoli