



Identifying high-risk AML in your patients

High-risk subtypes to consider when determining diagnosis and treatment

START



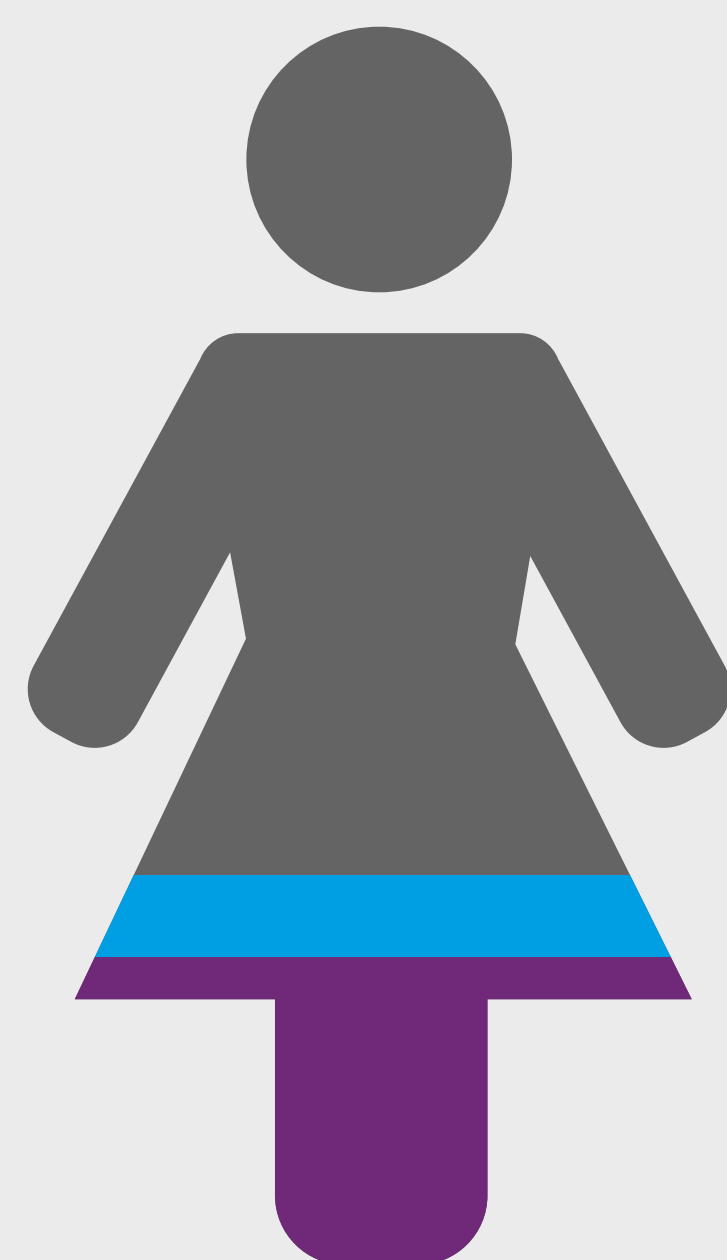
For patients >60 years old, the NCCN Guidelines[®] recommend selecting a treatment option based on patient performance status, comorbid conditions, and adverse features such as subtype rather than chronological age alone.¹

AML, acute myeloid leukemia.



Patients with high-risk AML have particularly poor outcomes

t-AML* and AML-MRC* are high-risk subtypes of AML²



t-AML

7%

of AML cases²
n = 3,055

AML-MRC

25%

of AML cases³
n = 2,740



Up to

1 in 3

AML patients
may fall into
these high-risk
categories^{2,3}

*As defined by WHO 2016 AML guidelines.

AML-MRC, AML with myelodysplasia-related changes; t-AML, therapy-related AML.



WHO 2016: classification of high-risk AML subtypes

**WHO
2016⁴**

AML: $\geq 20\%$ blasts in peripheral blood

AML-MRC

AML arising from a prior MDS or an MDS/MPN

OR

AML with an MDS-related cytogenetic abnormality

OR

AML with multilineage dysplasia

MORE DETAIL

t-AML

A distinct category of AML defined as: previously untreated AML with a history of prior cytotoxic treatment

MORE DETAIL

AML-MRC

t-AML



MATTHEW



Matthew

Male, 72 years old.
Enjoys gardening, and spending time
with his grandchildren.



Symptoms

Presented via his GP.
Fatigue, dyspnea, bone pain.



Clinical history

No prior hematologic disease
or cytotoxic therapy.



Blood work

WBC: $1.4 \times 10^9/L$; Hgb: 97 g/L;
platelets: $34 \times 10^9/L$

What tests would you order?





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Male, 72 years old.
Enjoys gardening, and spending time with his grandchildren.



Symptoms

Presented via his GP.
Fatigue, dyspnea, bone pain.



Clinical history

No prior hematologic disease or cytotoxic therapy.



Blood work

WBC: $1.4 \times 10^9/L$; Hgb: 97 g/L;
platelets: $34 \times 10^9/L$



Morphology

BM: myeloid blasts 22%



Cytogenetics

Complex karyotype
41, XY, del(5q), -8, -10, -12, -17, -21



Gene mutations

Wildtype: *NPM1*, *CEBPA*, *RUNX1*, *FLT3*, *TP53*, *ASXL1*, *IDH1/2*, *DDX41*, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *ZRSR2*
Mutation: *STAG2* and *U2AF1*

**How would you
classify this patient?**





MATTHEW



Matthew

Male, 72 years old.
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Symptoms

Presented via his GP.
Fatigue, dyspnea, bone pain.



Clinical history

No prior hematologic disease or cytotoxic therapy.



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Mutation: *STAG2* and *U2AF1*



Diagnosis according to AML classification:

WHO 2016: AML-MRC (AML with an MDS-related cytogenetic abnormality)
WHO 2022: AML-MR
ICC 2022: AML with MR gene mutations

Approximately **23%** of *de novo* AML patients present with cytogenetically defined AML-MRC^{6*}

AML-MRC occurs primarily in older patients, with a median age of 68 years, and is associated with a high frequency of adverse cytogenetics, including complex karyotype⁷

WHAT WOULD YOUR TREATMENT STRATEGY BE?



This case is not a real patient and may not be representative of all patients.

*As defined by WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th edition 2017.

AML-MR, AML myelodysplasia related; BM, bone marrow; GP, general practitioner; Hgb, hemoglobin; ICC, International Consensus Classification; WBC, white blood cells.

**Gordon**

Male, 68 years old.
Married, no children. Likes spending time with his dogs at the beach.

**Symptoms**

Presented via their GP.
Dyspnea, weight loss, petechiae.

**Clinical history**

No prior history of MDS, or cytotoxic therapy.

**Blood work**

WBC: $3.1 \times 10^9/L$; Hgb: 92 g/L;
platelets: $92 \times 10^9/L$

What tests would you order?





GORDON



Gordon

Male, 68 years old.
Married, no children. Likes spending time with his dogs at the beach.



Symptoms

Presented via their GP.
Dyspnea, weight loss, petechiae.



Clinical history

No prior history of MDS, or cytotoxic therapy.



Blood work

WBC: $3.1 \times 10^9/L$; Hgb: 92 g/L;
platelets: $92 \times 10^9/L$



Morphology

BM: myeloid blasts 36%
Confirmed multilineage dysplasia



Cytogenetics

46, XY, normal karyotype



Gene mutations

Wildtype: *NPM1*, *CEBPA*, *FLT3*, *TP53*, *IDH1/2*, *DDX4*, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *ZSRR2*
Mutation: *ASXL1*

**How would you
classify this patient?**





GORDON



Gordon

Male, 68 years old.
Married, no children. Likes spending time with his dogs at the beach.



Symptoms

Presented via their GP.
Dyspnea, weight loss, petechiae.



Clinical history

No prior history of MDS, or cytotoxic therapy.



Blood work

WBC: $3.1 \times 10^9/L$; Hgb: 92 g/L;
platelets: $92 \times 10^9/L$



Morphology

BM: myeloid blasts 36%
Confirmed multilineage dysplasia



Cytogenetics

46, XY, normal karyotype



Gene mutations

Wildtype: *NPM1*, *CEBPA*, *FLT3*, *TP53*, *IDH1/2*, *DDX4*, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *ZSR2*
Mutation: *ASXL1*



Diagnosis according to AML classification:

WHO 2016: AML-MRC (AML with multilineage dysplasia)
WHO 2022: AML-MR
ICC 2022: AML with MR gene mutations

Up to 80% of patients diagnosed with AML-MRC may have multilineage dysplasia^{8,9}

In a retrospective study of *de novo* AML cases without recurrent genetic rearrangements, *NPM1* or *biCEBPA* mutation, only 6% had multilineage dysplasia in the absence of AML-MRC cytogenetics⁶

WHAT WOULD YOUR TREATMENT STRATEGY BE?



**Julia**

Female, 52 years old.
Married, and has 2 children who
provide support.

**Symptoms**

Presented via the ER.
Fatigue, general weakness,
fever and pallor.

**Clinical history**

Diagnosed with MDS two
years prior, but refused
treatment.

**Blood work**

WBC: $2.9 \times 10^9/L$; Hgb: 95 g/L;
platelets: $95 \times 10^9/L$

**What tests would
you order?**





JULIA



Julia

Female, 52 years old.
Married, and has 2 children who provide support.



Symptoms

Presented via the ER.
Fatigue, general weakness, fever and pallor.



Clinical history

Diagnosed with MDS two years prior, but refused treatment.



Blood work

WBC: $2.9 \times 10^9/L$; Hgb: 95 g/L;
platelets: $95 \times 10^9/L$



Morphology

BM: myeloid blasts 40%



Cytogenetics

46, XX, del(5q)



Gene mutations

Wildtype: *NPM1*, *CEBPA*, *FLT3*, *TP53*, *IDH1/2*
Mutation: none

How would you classify this patient?





JULIA



Julia

Female, 52 years old.
Married, and has 2 children who provide support.



Symptoms

Presented via the ER.
Fatigue, general weakness, fever and pallor.



Clinical history

Diagnosed with MDS two years prior, but refused treatment.



Blood work

WBC: $2.9 \times 10^9/L$; Hgb: 95 g/L;
platelets: $95 \times 10^9/L$



Morphology

BM: myeloid blasts 40%



Cytogenetics

46, XX, del(5q)



Gene mutations

Wildtype: *NPM1*, *CEBPA*, *FLT3*, *TP53*, *IDH1/2*
Mutation: none



Diagnosis according to AML classification:

WHO 2016: AML-MRC (AML arising from prior MDS)
WHO 2022: AML-MR
ICC 2022: AML with MR cytogenetic abnormality

Almost 1 in 4 cases of AML is diagnosed in a patient under the age of 55 years¹⁰

Whilst the prognosis of younger patients is better, this demographic still accounts for approximately 10% of AML deaths.¹⁰

WHAT WOULD YOUR TREATMENT STRATEGY BE?





The classification of AML has been updated to reflect breakthroughs in disease understanding^{4,11,12}

The approved indication for VYXEOS is based on the WHO 2016 classification of AML⁴
The 2022 WHO and ICC classifications have revised the definition of AML-MRC and t-AML^{11,12}

WHO 2022¹¹

AML: ≥20% blasts in peripheral blood

AML-MR

De novo AML with ≥1 MDS-related cytogenetic abnormality

OR

De novo AML with an MDS-related somatic mutation in ≥1 of 8 genes: *ASXL1*, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*

OR

AML with a history of MDS or MDS/MPN with or without cytogenetic or somatic abnormalities

ICC 2022¹²

AML: ≥20% blasts in BM or peripheral blood
MDS/AML: 10–19% blasts in BM or peripheral blood

AML with MR cytogenetic abnormalities

OR

AML with MR gene mutations

AML with a mutation in ≥1 of 9 genes: *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*

OR

AML, progressed from MDS

A qualifier that can be applied to any subgroup or category to denote: AML arising from a prior MDS

MORE DETAIL

AML-pCT

A qualifier that can be applied to any subgroup or category to denote: AML with a history of prior chemotherapy, radiation therapy, or exposure to PARP1 inhibitors

AML, therapy related

A qualifier that can be applied to any subgroup or category to denote: AML with a history of prior chemotherapy, radiotherapy, or immune intervention

AML-MRC

t-AML

AML-pCT, AML post cytotoxic therapy.



Anti-leukemic regimens with curative intent start with intensive chemotherapy induction

VYXEOS is indicated for the treatment of adults with newly diagnosed therapy-related acute myeloid leukemia or AML with myelodysplasia-related changes.¹³



European LeukemiaNet 2022¹⁴

VYXEOS is recommended in the ELN 2022 guidelines for the treatment of patients diagnosed with t-AML and AML-MRC who are considered fit for intensive chemotherapy:

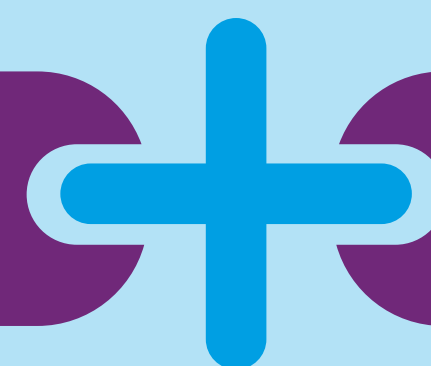
“Anthracyclines and cytarabine remain the backbone of intensive chemotherapy”

ELN 2022

Laying the foundation

Post hoc analysis suggests that VYXEOS provides optimal benefit when used for both induction and consolidation therapy¹⁵

INDUCTION



CONSOLIDATION



Important Safety Information

CLINICAL USE:

Pediatrics (<18 years): The safety and effectiveness of VYXEOS in the treatment of newly diagnosed t-AML and AML-MRC has not been established in children and adolescent patients under 18 years of age.

Geriatrics (≥65 years of age): No significant differences in safety were observed in patients aged 65 or older.

SERIOUS WARNINGS AND PRECAUTIONS:

VYXEOS has different dosage recommendations than daunorubicin hydrochloride injection, cytarabine injection, daunorubicin citrate liposome injection, and cytarabine liposome injection. Verify drug name and dose prior to preparation and administration to avoid dosing errors.

RELEVANT WARNINGS AND PRECAUTIONS:

- VYXEOS must not be substituted or interchanged with other daunorubicin and/or cytarabine containing products
- Tissue necrosis
- Cardiotoxicity is a known risk of anthracycline treatment
- Driving and operating machinery
- VYXEOS should be used in patients with a history of Wilson's disease or other copper-related disorder only if the benefits outweigh the risks. Discontinue VYXEOS in patients with signs or symptoms of acute copper toxicity
- Gastrointestinal mucositis and diarrhea
- Hematologic: Severe myelosuppression resulting in fatal infections and hemorrhage has been reported in patients after administration with VYXEOS. Patient blood counts should be regularly monitored during VYXEOS treatment and appropriate supportive measures should be used for clinical complications due to myelosuppression
- Hepatic impairment may increase the risk of toxicity associated with daunorubicin and cytarabine. Evaluation of hepatic function using conventional clinical laboratory tests is recommended prior to administration of VYXEOS and periodically during treatment. VYXEOS

should only be used in patients with severe hepatic impairment if the benefits outweigh the risks.

- Serious hypersensitivity reactions, including anaphylactic reactions have been reported with daunorubicin and cytarabine
- Increased susceptibility to infections
- Renal impairment may increase the risk of toxicity associated with daunorubicin and cytarabine. Evaluation of renal function using conventional clinical laboratory tests is recommended prior to administration of VYXEOS and periodically during treatment. VYXEOS should only be used in patients with end-stage renal disease if the benefits outweigh the risks
- Cardiac function and blood uric acid levels should be closely monitored. Appropriate therapy should be initiated if hyperuricemia develops
- Pregnancy: There are no data on the use of VYXEOS in pregnant women. Patients should be advised to avoid becoming pregnant during VYXEOS treatment. Male patients and women of childbearing potential must use effective methods of contraception during treatment and for 6 months following last dose of VYXEOS
- Male fertility may be compromised by treatment with VYXEOS according to animal studies
- Nursing women should be advised not to breastfeed during treatment with VYXEOS

FOR MORE INFORMATION:

Consult the VYXEOS Product Monograph at: www.jazzpharma.com for important information relating to adverse reactions, drug interactions, and dosing information that have not been discussed in this piece.

Further information for health care professionals can be found at www.vyxeos.ca.

The Product Monograph is also available by calling our medical department at: 1-800-520-5568.



References

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12. Arber DA, et al. *Blood* 2022;140:1200–28.
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