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PEER PERSPECTIVES

Continuity of care for patients treated with VYXEOS: Practices and management strategies

Hematology/Oncology Experts

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INDICATION

VYXEOS® (daunorubicin and cytarabine) is indicated for the treatment of newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adults and pediatric patients 1 year and older.

IMPORTANT SAFETY INFORMATION

WARNING: DO NOT INTERCHANGE WITH OTHER DAUNORUBICIN AND/OR CYTARABINE-CONTAINING PRODUCTS
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.

Contraindications

VYXEOS is contraindicated in patients with a history of serious hypersensitivity reactions to cytarabine, daunorubicin, or any component of the formulation.

Please see full Important Safety Information on page 24 and full Prescribing Information, including BOXED Warning.

Contents

Summary 3

1. Introduction 4

2. Secondary Acute Myeloid Leukemia **5**

2.1. Diagnostic challenges 5
2.2. Eligibility for intensive chemotherapy induction 5
2.3. Continuity of care throughout intensive chemotherapy treatment 6

3. Current treatments for sAML **7**

3.1. Overview of treatment options 7
3.2. VYXEOS 8

4. Practice strategies for managing sAML with VYXEOS at academic and community centers **13**

4.1. Classification of AML and identification of diagnostic qualifiers 14
4.2. Eligibility for intensive chemotherapy treatment 15
4.3. Induction with VYXEOS 16
4.4. Consolidation with VYXEOS 17
4.5. Allogeneic hematopoietic stem cell transplant 18

5. Continuity of care at academic and community centers and comanagement strategies **19**

5.1. Academic centers 19
5.2. Community centers 19
5.3. Models of comanagement between academic and community centers 20

6. Conclusions **23**

7. References **25**

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Summary

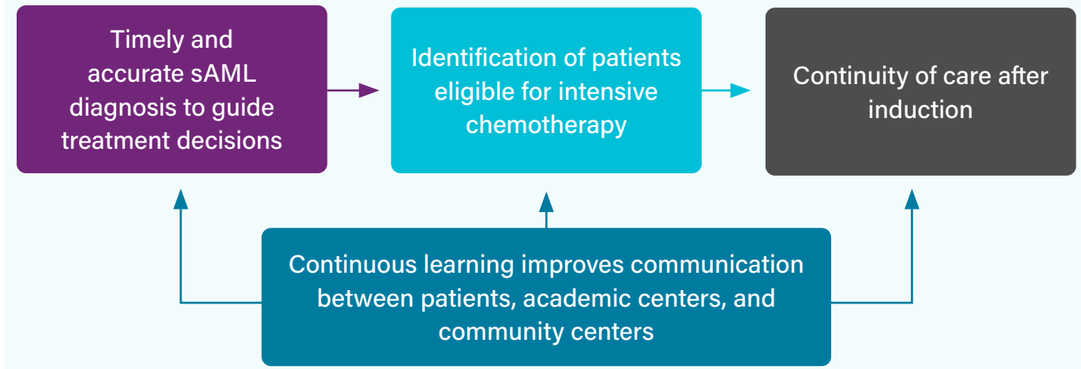
Secondary acute myeloid leukemia (sAML) comprises 3 main subtypes of AML: therapy-related AML, AML in the context of prior myeloid malignancy, and newly diagnosed AML with myelodysplasia-related changes.[1] sAML is a high-risk AML occurring primarily in older adults and is biologically and clinically different from *de novo* AML, resulting in substantially worse prognosis.[1-3] Intensive chemotherapy followed by hematopoietic stem-cell transplantation (HSCT) has curative potential and is the preferred treatment strategy for patients with sAML who are eligible for intensive chemotherapy and HSCT.[4] Daunorubicin and cytarabine (VYXEOS) is the preferred treatment option for patients ≥60 years with sAML who are eligible for intensive chemotherapy NCCN category 1 recommendation in NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines®]); for patients <60 years, daunorubicin and cytarabine (VYXEOS) has a category 2A National Comprehensive Cancer Network® (NCCN®) recommendation.[4] In a Phase 3 pivotal trial, VYXEOS demonstrated longer survival and higher overall remission rates compared with the traditional cytarabine for 7 days and daunorubicin for 3 days (7+3) regimen.[5]

Furthermore, VYXEOS treatment can be given in the outpatient setting[6] in both academic and community centers. This Peer Perspectives resource provides management strategies for the use of VYXEOS to help improve the outcomes of patients with sAML. Three clinicians who collaborate in treating patients with AML provided guidance and recommendations on the diagnosis, treatment, and management of AML. Recommendations provided by Dr Shah, Dr McCloskey, and Dr Abbas, the 3 experts contributing to this Peer Perspectives resource, are: 1) to initiate treatment once all diagnostic test results for sAML are available, if available; 2) to assess individual eligibility for intensive chemotherapy on the basis of patient's functional status, comorbidities, and risk of AML-related complications; 3) to adopt patient-centric approaches at academic and community centers, helping to ensure continuity of care throughout treatment stages. Establishing a culture of open communication between academic and community centers can foster trust and create a collaborative environment that helps to ensure efficient comanagement of sAML.

1. Introduction

sAML presents distinct diagnostic and treatment challenges, leading to strikingly worse prognoses compared with *de novo* AML.[1-3] The high-risk characteristics of these subtypes of AML contribute to 3 of the current treatment challenges: 1) timely and accurately diagnosing sAML to guide appropriate treatment selection; 2) identifying patients eligible for intensive chemotherapy on the basis of personalized assessment of functional status, comorbidities, and risk of sAML-related complications; 3) delivering seamless, collaborative care through outpatient treatment and partnership between academic and community centers (**Figure 1**). This Peer Perspectives resource provides approaches to consider when addressing these current challenges in managing sAML.

Figure 1. Current challenges in sAML treatment



2. Secondary Acute Myeloid Leukemia

sAML represents approximately 25% of all cases of AML,[7] with patients being generally older, with a worse performance status, and less likely to receive intensive chemotherapy than those with *de novo* AML.[3] Moreover, sAML is associated with high-risk cytogenetics and genetic mutations.[3,7-10] The general prognosis for patients with sAML has been described as "poor."[11]

2.1. Diagnostic challenges

"AML with myelodysplasia-related changes [AML-MRC] is absolutely underdiagnosed [in my experience] – I regularly see patients referred to me who have moved or come into our practice for whom AML-MRC was not previously recognized."
– Dr Abbas, large community hematology/oncology center

Establishing a proper sAML diagnosis is crucial for treatment selection.[12] Traditional classification of AML according to clinical ontogeny based solely on prior clinical records can lead to underdiagnosis or misdiagnosis of sAML,[9,13,14] and genomic and cytogenic analyses for specific gene mutations and chromosomal abnormalities are now recognized as essential for correct AML classification.[15]

2.2. Eligibility for intensive chemotherapy induction

Intensive chemotherapy for sAML offers the best chance of long-term survival, especially when followed by HSCT,[10,16-19] and is the preferred option for fit adults aged ≥60 years with high-risk AML eligible for intensive chemotherapy.[4]

"The goal [of treatment] is to achieve deep and rapid responses and allow patients to undergo transplant, if eligible, as an approach to cure."
– Dr McCloskey, leading academic hematology/oncology center

Despite the fact that many patients up to 80 years of age could be considered fit for intensive chemotherapy,[20,21] initial treatment decisions have historically been based largely on chronological age, with intensive induction chemotherapy traditionally reserved for patients aged <60 years.[4] This approach may prevent many patients with sAML from accessing potentially curative therapy.

Age alone should not be a barrier to intensive chemotherapy[22,23] and guidelines recommend that treatment selection in patients aged ≥60 years takes into consideration patient performance status, high-risk disease, and the presence of comorbidities. Comprehensive geriatric assessment models may also be utilized.[4]

2.3. Continuity of care throughout intensive chemotherapy treatment

Shifting intensive chemotherapy from inpatient to outpatient settings can create new opportunities for providing patient-centered care for sAML. This shift may bring potential benefits, such as improved quality of life, shorter travel distances, better opportunities for family/caregiver support, reduced risk of hospital infections, and savings in healthcare costs for both patients and providers.[19,24] Changing the paradigm by no longer restricting intensive chemotherapy to the inpatient setting may also facilitate continuity of intensive chemotherapy treatment through induction and consolidation, with or without allogeneic (allo)-HSCT; however, it is necessary to educate patients treated in the outpatient setting to monitor for and immediately report any possible serious complications, since myelosuppression is common and can be severe.[19,24]

With new opportunities for outpatient treatment both in academic and community centers, improved collaboration between these centers is needed to help optimize patient outcomes and ensure continuity of care throughout the disease continuum.[19] Lack of existing relationships between community and academic oncologists may be a barrier. Distrust can arise if clinicians perceive there is competition for patients.

3. Current treatments for sAML

3.1. Overview of treatment options

An overview of select sAML treatment options recommended by NCCN Guidelines® is shown in **Table 1**. For patients who are eligible to receive intensive chemotherapy, the preferred treatment options are 7+3 regimen for patients aged <60 years and daunorubicin and cytarabine (VYXEOS) for patients aged ≥60 years.

For patients who are ineligible to receive intensive induction, available treatments include hypomethylating agents (decitabine or azacitidine) with or without the B-cell lymphoma 2 inhibitor venetoclax, and low-dose cytarabine with venetoclax.[4]

Table 1. Overview of treatment options based on NCCN Guidelines for adult patients with sAML[a,4,6,25-31]

	Daunorubicin and cytarabine (VYXEOS)[a]	7+3[b]	VEN + HMA or LDAC	DEC	AZA
NCCN Category 1 recommendation[c]	✓[d]	✗[e]	✗	✗	✗
FDA-approved for newly diagnosed t-AML or AML-MRC	✓	✓	✗	✗	✗
Treatment duration	Up to 4 cycles[f]	Up to 2 cycles of induction followed by consolidation	Until PD/ unacceptable toxicity	Until PD/ unacceptable toxicity	Until PD/ unacceptable toxicity
Doses/cycle	2 or 3	7 or 10	33–38	3 or 5	7
Route of administration	IV	IV	Oral (VEN); SC/IV (HMA); IV (LDAC)	IV	SC/IV; Oral (ONU)
Feasibility of outpatient treatment	✓[g]	✗	✓	✓	✓

[a]Intravenous infusion over 90 minutes. Induction: cycle 1 on Days 1, 3, and 5 and cycle 2 (for patients without a response in cycle 1) on Days 1 and 3; consolidation (up to 2 cycles) on Days 1 and 3 of each cycle.[25] [b]Induction cycle 1: cytarabine administered by 7-day continuous infusion with daunorubicin on days 1 to 3; induction cycle 2 and consolidation cycles: cytarabine administered by 5-day continuous infusion with daunorubicin on days 1 and 2.[25] [c]NCCN Guidelines for induction-eligible patients with therapy-related AML other than CBF-AML, antecedent MDS/chronic myelomonocytic leukemia, patients with cytogenetic changes consistent with MDS (AML-MRC). Category 1 is based on high-level evidence and uniform consensus; it is one of 2 preferred treatments.[4] [d]Preferred for patients aged ≥60 years.[4] [e]Preferred for patients aged <60 years. 7+3, standard-dose cytarabine for 7 days and daunorubicin or idarubicin for 3 days.[4] [f]Up to 2 cycles of induction and 2 cycles of consolidation.[25] [g]Most patients in the Phase 3 study received induction in an inpatient setting.[6]

AML=acute myeloid leukemia; AZA=azacitidine; CBF=core binding factor; DEC=decitabine; FDA=US Food and Drug Administration; HMA=hypomethylating agent; IV=intravenous; LDAC=low-dose cytarabine; MDS=myelodysplastic syndromes; NCCN=National Comprehensive Cancer Network; PD=progressive disease; SC=subcutaneous; t-AML=therapy-related AML; VEN=venetoclax.

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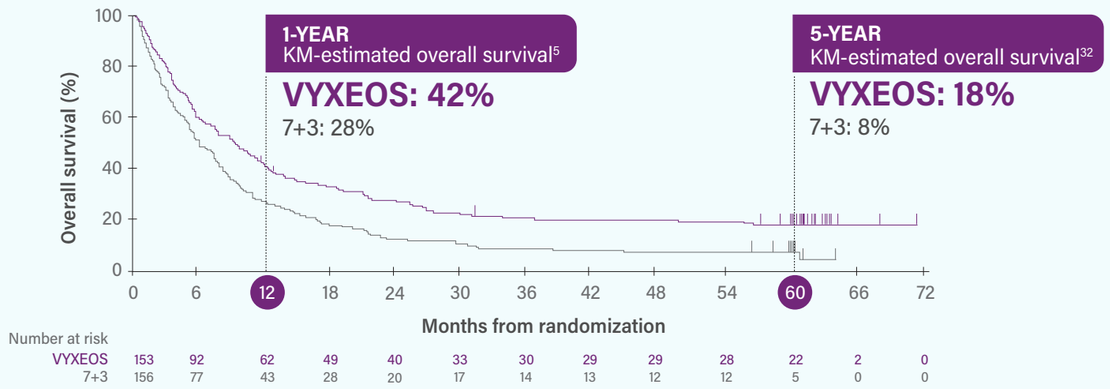
3.2. VYXEOS

VYXEOS is approved for the treatment of newly diagnosed therapy-related AML or AML-MRC in adults and pediatric patients ≥1 year.[24] Daunorubicin and cytarabine (VYXEOS) is the preferred treatment option for patients ≥60 years with sAML who are eligible for intensive chemotherapy (NCCN Category 1 recommendation).[4]

VYXEOS was investigated in a pivotal Phase 3, multicenter, open-label, randomized (1:1) study of VYXEOS vs 7+3 that included 309 patients with newly diagnosed high-risk/secondary AML. Patients were aged 60–75 years, previously untreated, eligible for intensive chemotherapy, and had an Eastern Cooperative Oncology Group performance status of 0 to 2.[5,32]

Figure 2. Survival rates in patients with sAML treated with VYXEOS vs 7+3 regimen[5,32]

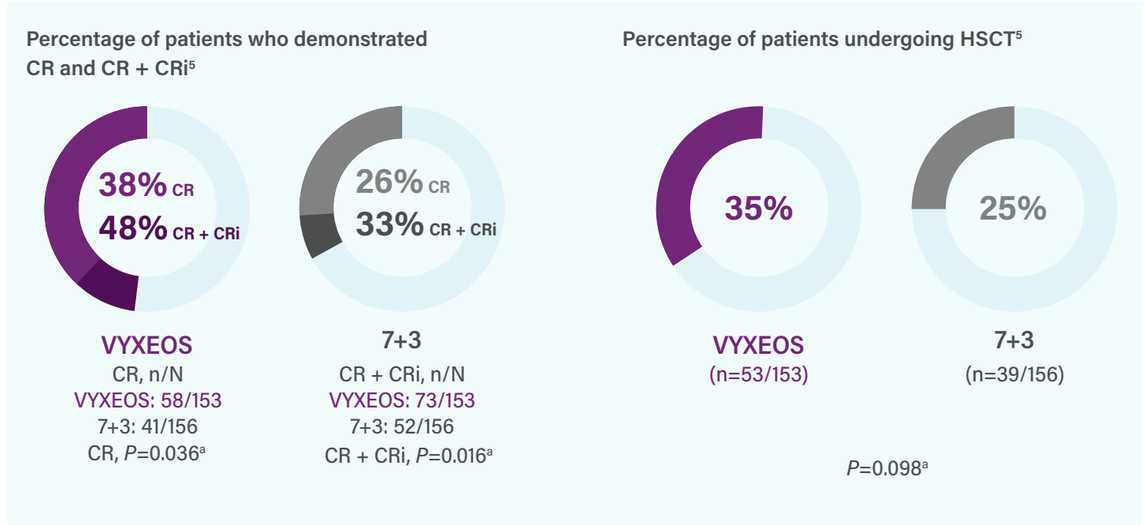


Reprinted from Lancet JE, et al. CPX-351 versus 7+3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial. *Lancet Haematol*. 2021;8(7):e481-e491, with permission from Elsevier.
This prospectively planned overall survival analysis of the ITT population was conducted on the basis of the final 5-year follow-up results from the Phase 3 study.[32]
ITT, intent-to-treat; KM, Kaplan-Meier.

VYXEOS demonstrated longer overall survival (**Figure 2**),[5,32] achieved higher complete remission rates (**Figure 3**),[5] and showed a higher proportion of patients proceeding to allo-HSCT (**Figure 3**) compared with conventional 7+3 therapy.[5]

After a median follow-up of approximately 5 years in each group, VYXEOS significantly improved the median overall survival (OS) compared with 7+3 regimen: 9.6 months with VYXEOS vs 5.9 months with 7+3, resulting in a 31% reduction in the risk of death (hazard ratio 0.69, 95% confidence interval (CI) 0.52–0.90], *P*=0.005).[25] The predicted 5-year OS more than doubled for patients treated with VYXEOS vs 7+3 (18% vs 8%) (**Figure 2**).[5,32]

Figure 3. Complete remission rates and HSCT rates for patients with sAML treated with VYXEOS vs 7+3 regimen[5]



[a]Two-sided *P* values.
CR, complete response; CRi, complete response with incomplete neutrophil or platelet recovery.

IMPORTANT SAFETY INFORMATION (cont'd)
Warnings and Precautions (cont'd)

Hypersensitivity Reactions

Serious or fatal hypersensitivity reactions, including anaphylactic reactions, have been reported with daunorubicin and cytarabine. Monitor patients for hypersensitivity reactions. If a mild or moderate hypersensitivity reaction occurs, interrupt or slow the rate of infusion with VYXEOS and manage symptoms. If a severe or life-threatening hypersensitivity reaction occurs, discontinue VYXEOS permanently, treat the symptoms, and monitor until symptoms resolve.

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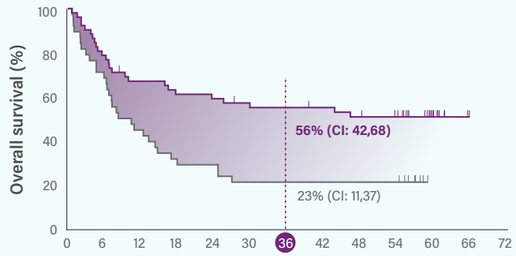
In a post hoc analysis of the Phase 3 study, survival benefit was demonstrated both for patients who underwent HSCT and those who had CR without HSCT.[33]

The post-HSCT 3-year OS estimate was 56% for VYXEOS and 23% for 7+3 (**Figure 4**).[32] Among patients who had CR or CRi, the post-HSCT 3-year OS estimate was 58% for VYXEOS and 29% for 7+3 (**Figure 4**).[32]

Figure 4. OS estimates post HSCT for patients with sAML treated with VYXEOS vs 7+3 regimen[32]

Analysis 1: KM curve for OS from time of HSCT[32]



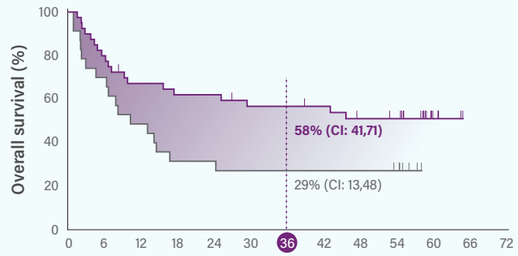
Number at risk

VYXEOS	53	42	35	32	31	28	28	27	24	21	6	0	0
7+3	39	27	18	12	12	9	9	9	9	8	0	0	0

Median OS (95% CI)[32]

VYXEOS:	7+3:
Not reached (16.2, NR) (n=23/53)	10.3 months (6.2, 16.7) (n=30/39)

Analysis 2: KM curve for OS from time of HSCT in patients who achieved CR or CRi[32]



Number at risk

VYXEOS	44	33	27	25	25	22	22	21	18	16	6	0	0
7+3	24	17	12	8	8	7	7	7	7	6	0	0	0

Median OS (95% CI)[32]

VYXEOS:	7+3:
Not reached (15.6, NR) (n=19/41)	11.7 months (4.6, 24.3) (n=17/24)

Reprinted from Lancet JE, et al. CPX-351 versus 7+3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial. *Lancet Haematol*. 2021;8(7):e481-e491, with permission from Elsevier.
3-year OS based on Kaplan-Meier estimates.[32]
NR, not reached.

Limitations of subanalyses[32]

- These exploratory post hoc subgroup analyses were not powered to determine statistical significance. No efficacy conclusions about OS following HSCT or OS following HSCT after CR or CRi can be drawn from these analyses
- Results should be interpreted with caution, as these analyses were not prespecified and were conducted in small, nonrandomized subgroups (Analysis 1, n=92; Analysis 2, n=65)
- The treatment effect of this nonrandomized subgroup was possibly confounded by unbalanced baseline characteristics
  - A higher proportion of patients proceeding to HSCT in the VYXEOS arm (75%) were in CR/CRi as compared with the 7+3 arm (62%)
  - To address this limitation, Analysis 2 evaluated only those patients in each treatment arm who were in CR/CRi at the time they received HSCT

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"In the patients who achieve a CR and then go on to transplant, relapse after transplant is [uncommon]." – Dr Shah, community hematology/oncology center

A summary of any grade adverse events occurring in ≥30% of patients in the VYXEOS arm is presented in **Table 2**.[25] The rates of most common adverse events of any grade were comparable between treatment arms, except for hemorrhage and rash, which were more frequent with VYXEOS.

Fatal treatment-emergent central nervous system hemorrhage not in the setting of progressive disease occurred in 2% of patients in the VYXEOS arm and in 0.7% of patients in the control arm.[25]

Time to recovery of neutrophil and platelet counts was longer for patients treated with VYXEOS than those treated with 7+3.[32] Blood counts should be monitored regularly, with platelet transfusions as required.[25]

IMPORTANT SAFETY INFORMATION (cont'd)
Warnings and Precautions (cont'd)

Copper Overload

VYXEOS contains copper. Consult with a hepatologist and nephrologist with expertise in managing acute copper toxicity in patients with Wilson's disease treated with VYXEOS. Monitor total serum copper, serum non–ceruloplasmin-bound copper, 24-hour urine copper levels, and serial neuropsychological examinations during VYXEOS treatment in patients with Wilson's disease or other copper-related metabolic disorders. Use only if the benefits outweigh the risks. Discontinue in patients with signs or symptoms of acute copper toxicity.

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Table 2. Most frequently reported adverse events (≥30% patients in the VYXEOS arm) in the pivotal Phase 3 study[25]

Adverse Reaction, n (%)	All Grades[a]		Grade ≥3[a]	
	VYXEOS (n=153)	7+3 (n=151)	VYXEOS (n=153)	7+3 (n=151)
Hemorrhage	107 (70)	74 (49)	15 (10)	9 (6)
Febrile neutropenia	104 (68)	103 (68)	101 (66)	102 (68)
Rash	82 (54)	55 (36)	8 (5)	2 (1)
Edema	78 (51)	90 (60)	2 (1)	5 (3)
Nausea	72 (47)	79 (52)	1 (1)	1 (1)
Diarrhea/colitis	69 (45)	100 (66)	4 (3)	10 (7)
Mucositis	67 (44)	69 (46)	2 (1)	7 (5)
Constipation	61 (40)	57 (38)	0	0
Musculoskeletal pain	58 (38)	52 (34)	5 (3)	4 (3)
Abdominal pain	51 (33)	45 (30)	3 (2)	3 (2)
Cough	51 (33)	34 (23)	0	1 (1)
Headache	51 (33)	36 (24)	2 (1)	1 (1)
Dyspnea	49 (32)	51 (34)	17 (11)	15 (10)
Fatigue	49 (32)	58 (38)	8 (5)	8 (5)
Arrhythmia	46 (30)	41 (27)	10 (7)	7 (5)

Full list of common adverse events can be found on the VYXEOS full Prescribing Information.[25]
[a]Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

IMPORTANT SAFETY INFORMATION (cont'd)
Warnings and Precautions (cont'd)

Tissue Necrosis
Daunorubicin has been associated with severe local tissue necrosis at the site of drug extravasation. Administer VYXEOS by the intravenous route only. Confirm patency of intravenous access before administration. Do not administer by intramuscular or subcutaneous route.

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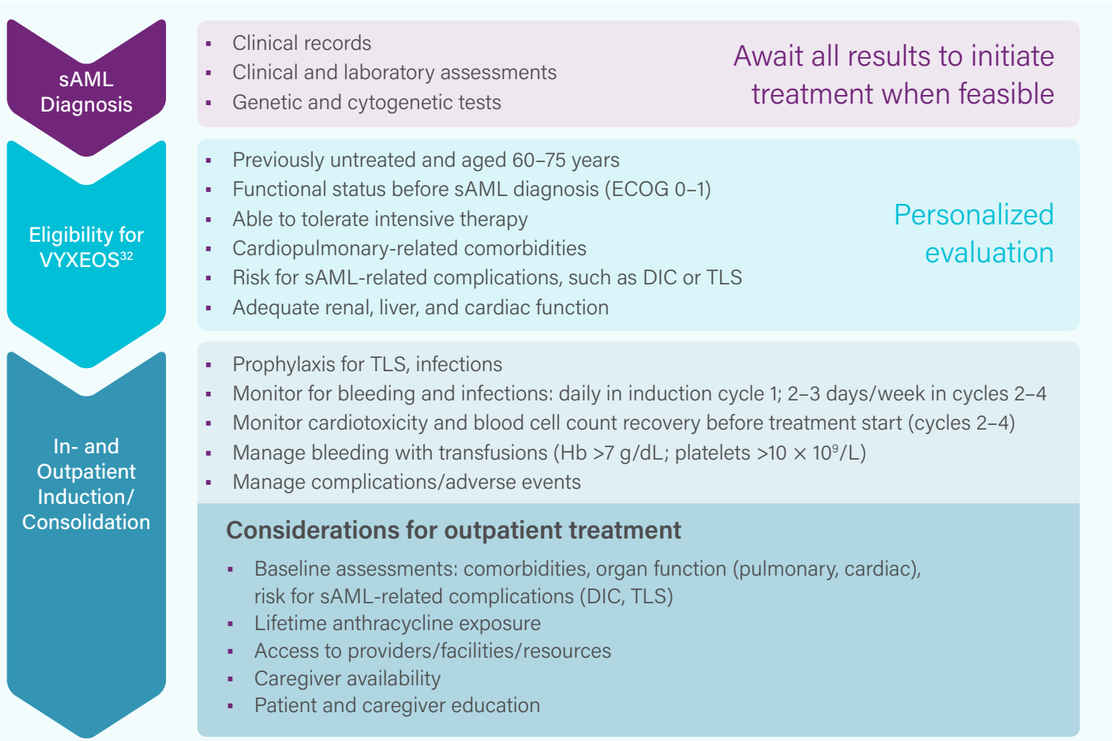
4. Practice strategies for managing sAML with VYXEOS at academic and community centers

While the 7+3 regimen requires a continuous intravenous infusion of cytarabine over 7 days plus daunorubicin on days 1, 2, and 3, VYXEOS is administered as a single intravenous infusion over 90 minutes.[25] Further, the availability of oral broad-spectrum antimicrobials and routine use of transfusions in the outpatient setting make it feasible for some patients, with careful monitoring, to receive VYXEOS therapy in the outpatient setting.[6]

As previously mentioned, consolidation with VYXEOS was administered in the outpatient setting for approximately half of the patients in the Phase 3 study.[6] Moreover, outpatient administration has been successfully implemented in the real world.[34] **Figure 5** summarizes practice strategies recommended by the experts contributing to this Peer Perspectives resource for managing treatment with VYXEOS at academic and community centers.

Figure 5. Summary of practice strategies for managing treatment with VYXEOS provided by the experts contributing to this Peer Perspectives resource



DIC, disseminated intravascular coagulation; Hb, hemoglobin; TLS, tumor lysis syndrome.

4.1. Classification of AML and identification of diagnostic qualifiers

The experts contributing to this Peer Perspectives resource believe that treatment decisions should be informed by clinical records as well as all the recommended clinical, laboratory, genetic, and cytogenetic assessments to minimize misdiagnosis, even if this entails a brief treatment delay. Currently, treatment for most patients begins before genetic test results are available,[4] but one large study (n=4700) found that even a delay of 15 days or more between diagnosis and treatment start had not demonstrated negative effects on prognosis in most patients with AML.[35] The experts participating in this Peer Perspectives resource argue that initiating treatment promptly should not preclude accurate diagnosis as long as patients are stable, ensuring that all eligible patients have the option for potentially curative therapy.

"I do have the perception that sAML is underdiagnosed in the rush to proceed with treatment." – Dr McCloskey, leading academic hematology/oncology center

For patients with prior myelodysplastic syndromes (MDS), fluorescence in situ hybridization (FISH) and cytogenetics can be available within 48 hours and targeted sequencing in 2–3 days; contracted-out next-generation sequencing might take 3–10 days. Treatment initiation should await all results if the patient is stable.

"Provided that the patient is stable, it is crucial to await full pathology, molecular, and cytogenetic results to make proper diagnosis." – Dr McCloskey, leading academic hematology/oncology center

"FISH with AML and MDS panels has identified many patients with AML-MRC–defining cytogenetics, making them eligible for VYXEOS treatment." – Dr Abbas, leading academic hematology/oncology center

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4.2. Eligibility for intensive chemotherapy treatment

Hematologist-oncologists play a key role in identifying patients with sAML who may benefit from intensive chemotherapy such as VYXEOS. While age is a factor, eligibility is multifactorial.

"We consider induction routinely for all patients under 75." – Dr McCloskey, leading academic hematology/oncology center

To determine eligibility for intensive chemotherapy, carefully assess the patient's functional status in the weeks or months before sAML diagnosis, evaluate comorbid conditions and disease-related complications, and monitor pulmonary and cardiac function. Additionally, inform your treatment decisions by understanding the patient's treatment goals and the aspects of life they value most.

"It is important to understand the patient's functional status several weeks or months before their sAML diagnosis." – Dr Shah, community hematology/oncology center

4.3. Induction with VYXEOS

VYXEOS induction comprises an initial cycle followed by a second cycle only if CR is not demonstrated and lifetime anthracycline exposure allows.[25]

Experts participating in this Peer Perspectives resource advise monitoring inpatients daily for infections and bleeding complications. Prophylactic medication typically includes allopurinol for tumor lysis syndrome (TLS) as well as antifungals, antivirals, and antibiotics for a range of infections.[36]

Blood counts are managed with transfusions to maintain hemoglobin concentration >7 g/dL and platelet concentration >10 × 10^9/L. It is critical to respond to signs of infection with urgent diagnostic workup and prompt initiation of intravenous antibiotics in the event of febrile neutropenia. Guidelines from the American Society of Clinical Oncology advise transfusion at higher levels in patients with signs of hemorrhage, high fever, hyperleukocytosis, rapid fall of platelet count, or coagulation abnormalities.[37]

"At my institution, we administer liposomal daunorubicin and cytarabine induction on an outpatient basis in some cases and to all patients receiving consolidation.[34]"
– Dr Kasner, leading academic hematology/oncology center

Experts from academic centers believe induction may also be initiated safely in the outpatient setting, depending upon patients' baseline comorbidities, organ function, risk for disease-related complications (eg, disseminated intravascular coagulation and TLS), distance to hospital, and the availability of a caregiver. According to one published strategy, outpatients attend the center daily during the 5-day induction for laboratory tests and fluids as needed; subsequent visits are 2–3 times per week as necessary.[34]

Experts from community centers usually perform VYXEOS induction in the inpatient setting. Daily monitoring for infections and bleeding complications, and use of transfusions and prophylactic medications will be similar to that in academic centers. Individual centers may have additional strategies to prevent complications, such as to reduce the risk of deep vein thrombosis and infections and aggressive oral care to prevent severe mucositis.

IMPORTANT SAFETY INFORMATION (cont'd)
MOST COMMON ADVERSE REACTIONS

The most common adverse reactions (incidence ≥25%) are hemorrhagic events (74%), febrile neutropenia (70%), rash (56%), edema (55%), nausea (49%), mucositis (48%), diarrhea (48%), constipation (42%), musculoskeletal pain (43%), fatigue (39%), abdominal pain (36%), dyspnea (36%), headache (35%), cough (35%), decreased appetite (33%), arrhythmia (31%), pneumonia (31%), bacteremia (29%), chills (27%), sleep disorders (26%), and vomiting (25%).

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4.4. Consolidation with VYXEOS

Patient monitoring and toxicity management during VYXEOS outpatient consolidation is the same as for outpatient induction. Additional education of outpatients to prevent infections and bleeding complications is crucial.

Of note, in the Phase 3 study, consolidation with VYXEOS was administered completely in the outpatient setting for 51% (n=25) of patients during the first cycle and for 61% (n=14) of patients during the second cycle,[6] showing that outpatient treatment with VYXEOS is feasible for many patients.

"At my institution, implementation of an outpatient approach requires that patients have quick, easy access to providers."
– Dr Kasner, leading academic hematology/oncology center[34]

In Dr Abbas' community practice at Tennessee Oncology, nurse practitioners and physician assistants monitor patients twice weekly during consolidation in order to provide prompt supportive care if needed and detect complications early.

"In my experience, patients can usually be stabilized and transitioned to the outpatient setting to receive VYXEOS as outpatient."
– Dr Abbas, large community hematology/oncology center

The experts participating in this Peer Perspectives resource recommend that, in anticipation of the need for transfusions, arrangements should be in place with the blood bank ahead of time, typically if hemoglobin concentrations fall below 7 g/dL and platelet concentrations drop below 15 × 10^9/L. Furthermore, at the earliest signs of complications, including neutropenic fever, sepsis, or dehydration, patients need to be admitted to the hospital immediately. Education on the signs and symptoms of neutropenic fever and on what to expect from likely emergency department (ED) visits is needed for outpatients.

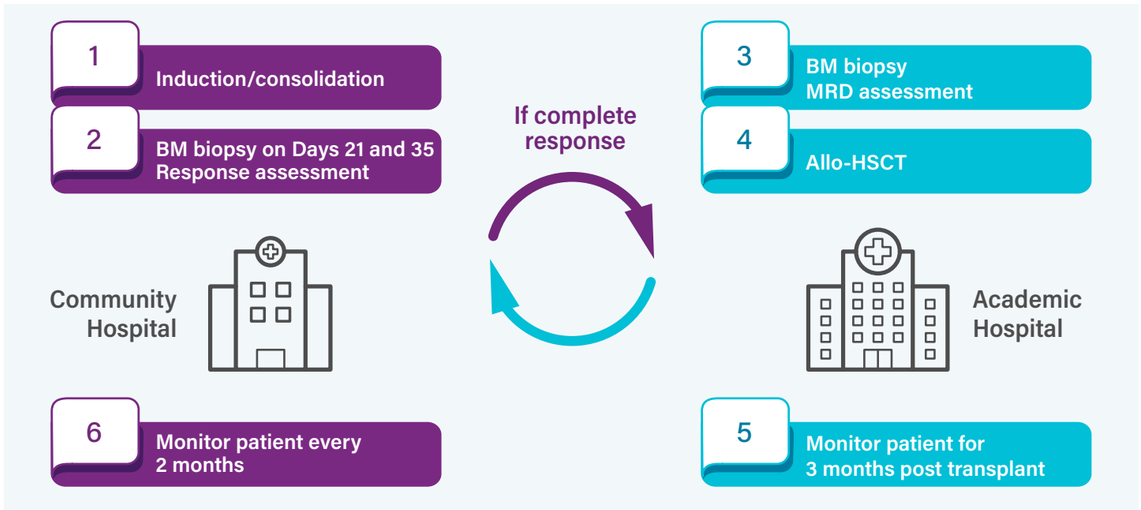
"Overall, in my practice, the number 1 way we prevent and manage complications in the outpatient setting is with very thorough assessment and communication between the advanced practice providers and the physicians who are seeing the patient." – Dr Shah, community hematology/oncology center

4.5. Allogeneic hematopoietic stem cell transplant

Similar to AML, allo-HSCT remains the gold standard for patients with sAML. Allo-HSCT should be performed as soon as a patient demonstrates CR, is confirmed to have no disease complications, and a caregiver is in place.

In one expert's practice setting, bone marrow biopsies are performed on Day 21 and Day 35 after completion of VYXEOS induction and consolidation. Once CR is confirmed, patients are transferred to an academic center. The academic center will take another bone marrow biopsy to document measurable residual disease status before proceeding with the allo-HSCT. In this practice example, the patient is then monitored at the transplant center for 3 months before returning to the care of the community center, where they are monitored every 2 months for cytopenias, transfusion support, relapse, and graft versus host disease (**Figure 6**). This collaborative approach may ensure seamless care for patients with sAML throughout their treatment journey.

Figure 6. Comanagement during allo-HSCT



allo-HSCT, allogeneic hematopoietic stem cell transplant; BM, bone marrow; MRD, measurable residual disease.

5. Continuity of care at academic and community centers and comanagement strategies

5.1. Academic centers

The experts participating in this Peer Perspectives resource believe that effective collaboration between community and academic centers is crucial for helping to ensure continuity of care for patients with sAML throughout their treatment journey, from induction and consolidation to allo-HSCT. Any center that is capable of 7+3 induction can administer VYXEOS; ideally, centers have subspecialized teams to support all aspects of patient care.

Continuity of care for outpatient induction relies on teamwork and the hospital's logistical arrangements. For example, in one expert's academic center, an outpatient with a fever would present to the ED, where a predefined set of procedures and tests would be available and they could be moved directly to a reserved leukemia bed.

5.2. Community centers

"I typically manage all of care through induction and consolidation except for the up-front allo-HSCT referral to an academic center."
– Dr Abbas, large community hematology/oncology center

Community centers with sufficient numbers of healthcare professionals and outpatient infrastructures to provide urgent transfusion support, infection treatment, and high-acuity inpatient care can administer induction, helping to ensure continuity of care (**Table 3**).

It is important to assess your center's capabilities to identify any potential limitations, such as lack of intensive care units, and transport to outpatient facilities. Collaboration with academic centers is critical to success.

Table 3. Considerations for community centers undertaking VYXEOS induction and consolidation

VYXEOS induction and consolidation in community centers: organizational considerations
▪ Collaboration between community-based oncologists and advising academic leukemia specialists as part of comanagement approaches
▪ Advanced practice provider availability for laboratory monitoring and clinical evaluation multiple times a week and for provision of same-day hydration, IV antibiotics, and transfusions
▪ Blood bank support for same-day transfusions of packed red blood cells and platelets
▪ Emergency evaluation and treatment of complications such as neutropenic fever or sepsis
▪ Triage system for incoming calls to expedite office evaluation of patients and allow rapid clinical evaluation by the primary healthcare team, helping to avoid ED visits
▪ Prespecified instructions for the ED to ensure prompt and appropriate workup, IV antibiotic treatment, and hospital admission
▪ Patient education on complications and procedures
▪ Patient screening for caregiver support and transport arrangements
▪ Robust standard operating protocols

5.3. Models of comanagement between academic and community centers

"I honestly believe that the reason behind the incredibly high rate of remissions and overall survival for our patients is because of the collaborative care they are receiving in our community-based cancer program."
– Dr Shah, community hematology/oncology center

Comanagement offers significant benefits for both community and academic centers by facilitating continuity of care through induction, consolidation, and allo-HSCT (**Table 4**). At minimum, community centers need access to advice from academic centers on individual cases and access to transplant centers, and academic centers rely on community centers for patient monitoring, transfusions, and complications management.

"Such collaborations can help improve patient outcomes and can allow for more prompt transplant planning."
– Dr McCloskey, leading academic hematology/oncology center

In the experts' experience, collaborative comanagement not only may improve patient outcomes, but also may facilitate timely planning for allo-HSCT, which should not be delayed once the first CR is demonstrated.

Table 4. Collaborative arrangement: potential setting for VYXEOS treatment provision

	Academic centers	Community centers
Diagnosis	Yes ▪ Usually more in-house provision of specialist tests vs community centers	Yes ▪ Specialist tests may be contracted out
VYXEOS induction	Yes	Yes
VYXEOS consolidation	Yes	Yes
Routine outpatient monitoring, transfusions, and toxicity management	Usually the responsibility of community centers	Yes
Assessment of remission status	Yes	Yes
MRD assessment	Yes	Currently, the analyses are conducted at or coordinated by academic centers or sent out via labs
Allo-HSCT	Yes ▪ Evaluation and transplant procedures	Patients are referred to an academic or transplant center if prior evaluation suggests HSCT may be an option
Maintenance therapy	Usually the responsibility of community centers ▪ Will assist with maintenance treatment plan	Yes

IMPORTANT SAFETY INFORMATION (cont'd)
Warnings and Precautions

Hemorrhage
Serious or fatal hemorrhage events, including fatal CNS hemorrhages, associated with prolonged thrombocytopenia, have occurred with VYXEOS. The overall incidence (grade 1-5) of hemorrhagic events was 74% in the VYXEOS arm and 56% in the control arm. The most frequently reported hemorrhagic event was epistaxis (36% in VYXEOS arm and 18% in control arm). Grade 3 or greater events occurred in 12% of VYXEOS treated patients and in 8% of patients in the control arm. Fatal treatment-emergent CNS hemorrhage not in the setting of progressive disease occurred in 2% of patients in the VYXEOS arm and in 0.7% of patients in the control arm. Monitor blood counts regularly and administer platelet transfusion support as required.

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"Effective collaboration hinges on establishing direct and ongoing communication, using efficient modes of interaction, and sharing center protocols as first steps."
– Dr McCloskey, leading academic hematology/oncology center

Establishing a framework for comanagement may seem daunting, but the experts participating in this Peer Perspectives have built successful partnerships between academic and community centers. **Table 5** illustrates some fundamental considerations for comanagement strategies.

Table 5. Fundamental elements of comanagement strategies

Considerations for successful comanagement of VYXEOS treatment between academic and community centers
▪ Transparent and open lines of communication among multidisciplinary teams within and between centers, as well as with patients and caregivers — Agreed ways of communication (eg, telephone, secure messaging, in-person meetings, e-consultations, virtual consultations)
▪ An understanding of the experience and capabilities of each practice and any regional variations in practices
▪ Sharing of protocols
▪ A culture of collaboration and trust rather than a hierarchy of care
▪ An established and consistent workflow that works for both centers (eg, an arrangement for all bone marrow evaluations and transplant consultations to be done at the academic center)
▪ Agreement on which patient consultations should be held jointly, potentially with the inclusion of the transplant team (eg, the first visit and the postremission visit)
▪ Clear goals of treatment and expectations for each patient
▪ A defined treatment plan for each patient that is shared and understood by healthcare professionals at both academic and community centers, patients, and caregiver
▪ An action plan for emergencies
▪ Consistent patient and caregiver education

6. Conclusions

Hematologist-oncologists play a crucial role in improving outcomes for patients with sAML. The standard of care for these intensive treatment–eligible adult patients is intensive chemotherapy and HSCT, which has curative potential.[10,18,19] VYXEOS is an intensive chemotherapy that can offer patients (see section 4.3) the opportunity to receive induction and consolidation in the outpatient setting, making this potentially curative regimen more accessible. The experts participating in this Peer Perspectives resource believe that proper sAML diagnosis, including genomic and cytogenetic tests, should be completed before treatment start. Assessing each patient's functional status, comorbidities, and risk of sAML-related complications is essential to identifying patients who may benefit from treatment with VYXEOS. Collaborations between academic and community centers are central to continuity of care and have already been created successfully in some regions. The experts encourage all centers to forge and strengthen these relationships, which are key to help improving the care and prognosis of patients with sAML treated with VYXEOS.

IMPORTANT SAFETY INFORMATION (cont'd)
Warnings and Precautions (cont'd)

Cardiotoxicity

VYXEOS contains daunorubicin, which has a known risk of cardiotoxicity. This risk may be increased in patients with prior anthracycline therapy, preexisting cardiac disease, previous radiotherapy to the mediastinum, or concomitant use of cardiotoxic drugs. Assess cardiac function prior to VYXEOS treatment and repeat prior to consolidation and as clinically required. Discontinue VYXEOS in patients with impaired cardiac function unless the benefit of initiating or continuing treatment outweighs the risk. VYXEOS is not recommended in patients with cardiac function that is less than normal.

Total cumulative doses of non-liposomal daunorubicin greater than 550 mg/m^2 have been associated with an increased incidence of drug-induced congestive heart failure. The tolerable limit appears lower (400 mg/m^2) in patients who received radiation therapy to the mediastinum. Calculate the lifetime cumulative anthracycline exposure prior to each cycle of VYXEOS. VYXEOS is not recommended in patients whose lifetime anthracycline exposure has reached the maximum cumulative limit.

Please see full Important Safety Information on page 24 and full Prescribing Information, including BOXED Warning.

INDICATION

VYXEOS® (daunorubicin and cytarabine) is indicated for the treatment of newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adults and pediatric patients 1 year and older.

IMPORTANT SAFETY INFORMATION

WARNING: DO NOT INTERCHANGE WITH OTHER DAUNORUBICIN AND/OR CYTARABINE-CONTAINING PRODUCTS

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.

Contraindications

VYXEOS is contraindicated in patients with a history of serious hypersensitivity reactions to cytarabine, daunorubicin, or any component of the formulation.

Warnings and Precautions

Hemorrhage

Serious or fatal hemorrhage events, including fatal CNS hemorrhages, associated with prolonged thrombocytopenia, have occurred with VYXEOS. The overall incidence (grade 1-5) of hemorrhagic events was 74% in the VYXEOS arm and 56% in the control arm. The most frequently reported hemorrhagic event was epistaxis (36% in VYXEOS arm and 18% in control arm). Grade 3 or greater events occurred in 12% of VYXEOS treated patients and in 8% of patients in the control arm. Fatal treatment-emergent CNS hemorrhage not in the setting of progressive disease occurred in 2% of patients in the VYXEOS arm and in 0.7% of patients in the control arm. Monitor blood counts regularly and administer platelet transfusion support as required.

Cardiotoxicity

VYXEOS contains daunorubicin, which has a known risk of cardiotoxicity. This risk may be increased in patients with prior anthracycline therapy, preexisting cardiac disease, previous radiotherapy to the mediastinum, or concomitant use of cardiotoxic drugs. Assess cardiac function prior to VYXEOS treatment and repeat prior to consolidation and as clinically required. Discontinue VYXEOS in patients with impaired cardiac function unless the benefit of initiating or continuing treatment outweighs the risk. VYXEOS is not recommended in patients with cardiac function that is less than normal.

Total cumulative doses of non-liposomal daunorubicin greater than 550 mg/m^2 have been associated with an increased incidence of drug-induced congestive heart failure. The tolerable limit appears lower (400 mg/m^2) in patients who received radiation therapy to the mediastinum. Calculate the lifetime cumulative anthracycline exposure prior to each cycle of VYXEOS. VYXEOS is not recommended in patients whose lifetime anthracycline exposure has reached the maximum cumulative limit.

Hypersensitivity Reactions

Serious or fatal hypersensitivity reactions, including anaphylactic reactions, have been reported with daunorubicin and cytarabine. Monitor patients for hypersensitivity reactions. If a mild or moderate hypersensitivity reaction occurs, interrupt or slow the rate of infusion with VYXEOS and manage symptoms. If a severe or life-threatening hypersensitivity reaction occurs, discontinue VYXEOS permanently, treat the symptoms, and monitor until symptoms resolve.

Copper Overload

VYXEOS contains copper. Consult with a hepatologist and nephrologist with expertise in managing acute copper toxicity in patients with Wilson's disease treated with VYXEOS. Monitor total serum copper, serum non-ceruloplasmin-bound copper, 24-hour urine copper levels, and serial neuropsychological examinations during VYXEOS treatment in patients with Wilson's disease or other copper-related metabolic disorders. Use only if the benefits outweigh the risks. Discontinue in patients with signs or symptoms of acute copper toxicity.

Tissue Necrosis

Daunorubicin has been associated with severe local tissue necrosis at the site of drug extravasation. Administer VYXEOS by the intravenous route only. Confirm patency of intravenous access before administration. Do not administer by intramuscular or subcutaneous route.

Embryo-Fetal Toxicity

VYXEOS can cause embryo-fetal harm when administered to a pregnant woman. Patients should avoid becoming pregnant while taking VYXEOS. If VYXEOS is used during pregnancy or if the patient becomes pregnant while taking VYXEOS, apprise the patient of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of VYXEOS.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions (incidence ≥25%) are hemorrhagic events (74%), febrile neutropenia (70%), rash (56%), edema (55%), nausea (49%), mucositis (48%), diarrhea (48%), constipation (42%), musculoskeletal pain (43%), fatigue (39%), abdominal pain (36%), dyspnea (36%), headache (35%), cough (35%), decreased appetite (33%), arrhythmia (31%), pneumonia (31%), bacteremia (29%), chills (27%), sleep disorders (26%), and vomiting (25%).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. You may also report side effects to Jazz Pharmaceuticals at 1-800-520-5568.

Please see full Prescribing Information, including BOXED WARNING

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Vyxeos® (daunorubicin and cytarabine) 44 mg/100 mg per vial liposome for injection

Vyxeos® (daunorubicin and cytarabine) 44 mg/100 mg per vial liposome for injection

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