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TREATMENT IN HIGH-RISK* ACUTE MYELOID LEUKEMIA (AML): TRANSLATING CLINICAL TRIAL EFFICACY INTO REAL-WORLD EFFECTIVENESS

Introduction

Vyxeos liposomal® (daunorubicin 44 mg/cytarabine 100 mg, formerly known as CPX-351; Jazz Pharmaceuticals) is the first chemotherapy to significantly increase median overall survival (OS) vs conventional chemotherapy (cytarabine and daunorubicin; 7+3/5+2) in patients with high-risk* AML.[1,2] Vyxeos liposomal is an advanced dual-drug liposomal formulation of daunorubicin and cytarabine, which animal models have shown optimizes drug delivery to the bone marrow, in a fixed 1:5 molar ratio that has been shown in vitro and in vivo to maximize synergistic antitumor activity in AML.[1] Vyxeos liposomal is indicated for the treatment of adults with newly diagnosed, therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC), henceforth referred to as high-risk AML.[1]

In the pivotal, randomized, multicenter, phase 3 study, Vyxeos liposomal[1] demonstrated superior overall survival (OS; primary outcomes) and higher remission outcomes vs conventional 7+3 chemotherapy.[2] The study included elderly patients (60–75 years of age) with high-risk* AML.[2] Patients (N=309) were randomly assigned 1:1 to receive Vyxeos liposomal or 7+3 therapy for up to two induction cycles and up to two consolidation cycles of the same regimen.[2] With a median follow-up of 20.7 months, Vyxeos liposomal treatment significantly improved median OS vs 7+3 therapy (Kaplan–Meier estimated median OS: 9.56 vs 5.95 months, respectively; hazard ratio [HR]: 0.69; 95% confidence interval [CI]: 0.52–0.90; 2-sided P=0.005).[1,2] Treatment with Vyxeos liposomal was also associated with a significantly higher overall remission rate (complete remission [CR] or CR with incomplete neutrophil or platelet recovery [CRi]) vs 7+3 therapy (47.7% vs 33.3%; 2-sided P=0.016) and CR rate (37.3% vs 25.6%; 2-sided P=0.040).[2] Post hoc exploratory analyses also showed improved survival and response outcomes across age strata and AML subtypes.[2]

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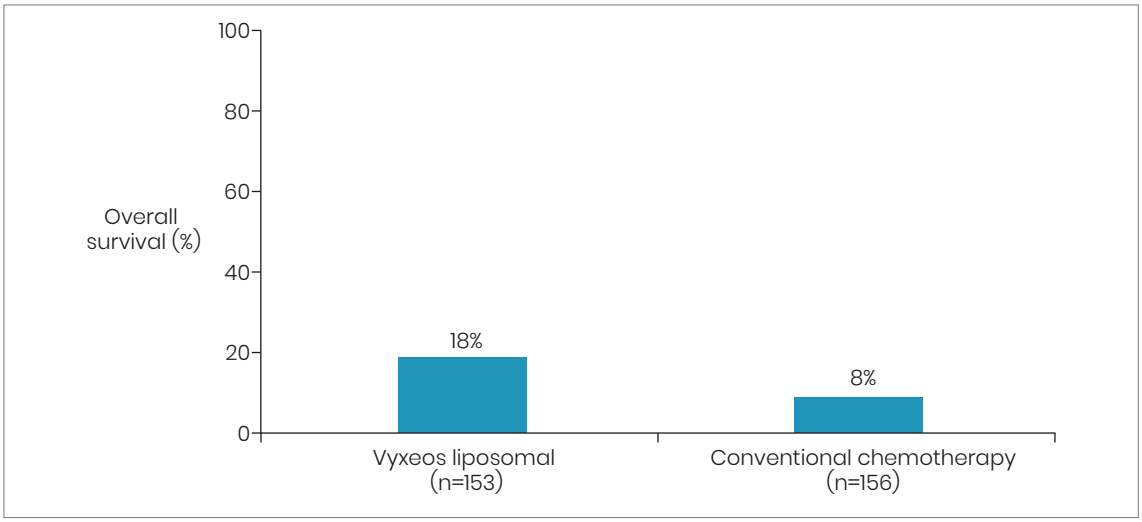
The overall frequency and severity of non-hematologic adverse events were comparable between the two arms, despite a longer treatment phase and prolonged time to neutrophil and platelet count recovery (in responders after initial induction) with Vyxeos liposomal (median: 35 and 36.5 days, respectively) vs 7+3 therapy (median: 29 and 29 days, respectively).[2] Prolonged thrombocytopenia and neutropenia is consistent with prolonged myelosuppression and patients may require additional monitoring.[1,2] The most frequently reported adverse events (Grade 3–5) in the Vyxeos liposomal and 7+3 treatment groups were febrile neutropenia (68% vs 70.9%), pneumonia (19.6% vs 14.6%), and hypoxia (13.1% vs 15.2%).[2] Early mortality rates with Vyxeos liposomal and 7+3 treatment were 5.9% and 10.6% (two-sided P=0.149) through Day 30 and 13.7% and 21.2% (two-sided P=0.097) through Day 60.[2]

Five-year follow-up data from the pivotal Vyxeos liposomal study

Evidence of long-term treatment outcomes in patients with secondary AML is limited. In a prespecified final analysis of OS in the intent-to-treat population of the pivotal phase 3 clinical trial of Vyxeos liposomal, patients were followed until death or for 5 years post-randomization.[4] The objective was to provide insights into the long-term efficacy of Vyxeos liposomal treatment in adults with newly diagnosed, high-risk* AML.

Overall, 5-year results demonstrated significantly improved OS with Vyxeos liposomal vs 7+3 therapy, with a median OS of 9.33 vs 5.95 months (HR: 0.70; 95% CI: 0.55–0.91) and a 5-year OS rate of 18% vs 8%, respectively (**Figure 1**).[4] At a median follow-up of 60.91 months in the Vyxeos liposomal arm and 59.93 months in the 7+3 therapy arm, post hoc exploratory analyses showed a median OS in patients 60–69 years of age was 9.59 months in patients receiving Vyxeos liposomal and 6.87 months in patients given 7+3 therapy (HR: 0.73; 95% CI: 0.54–0.99).[4] For patients 70–75 years of age, the median OS was 8.87 months vs 5.62 months with Vyxeos liposomal and 7+3 therapy, respectively (HR: 0.52; 95% CI: 0.34–0.77).[4]

Figure 1. Kaplan–Meier estimates of overall survival for the Vyxeos liposomal treatment arm vs the 7+3 treatment arm after 5-years of follow-up in the phase 3 clinical trial in adults with untreated high-risk* AML (intent-to-treat population).[4†]



†Vyxeos liposomal, median follow-up 60.91 months; conventional chemotherapy, median follow-up 59.93 months.

Several additional post hoc exploratory analyses were also performed.[4] Firstly, among patients who achieved remission, OS was improved at both years 3 and 5 with Vyxeos liposomal compared with conventional chemotherapy: 36% vs 23%, respectively, at 3 years, and 30% vs 19% at 5 years.[4] Secondly, the proportions of patients proceeding to allogeneic hematopoietic stem cell transplantation (HSCT) were 35% (53/153) in the Vyxeos liposomal arm and 25% (39/156) in the conventional chemotherapy arm.[4] Thirdly, OS in patients who received Vyxeos liposomal and underwent HSCT was maintained above 50% at 5 years post-randomization.[4]

No long-term adverse event data were collected beyond that reported in the primary endpoint analysis, except for mortality. In this long-term analysis, the rate of all-cause mortality was lower with Vyxeos liposomal treatment than with 7+3 therapy (81% vs 93%).[4]

Overall, the authors concluded that the improved OS observed with Vyxeos liposomal compared with conventional chemotherapy in adult patients who had remission, as well as those who underwent HSCT, suggests potentially deeper responses may be achievable with Vyxeos liposomal treatment.[4]

Real-world experience from an Italian compassionate use program

A key question for clinicians is how the survival and remission benefits of Vyxeos liposomal vs conventional chemotherapy demonstrated in high-risk* AML clinical trials translate to a more heterogenous patient population treated in routine clinical practice.[5] To address this, investigators evaluated the clinical activity of Vyxeos liposomal in a study of 71 elderly patients (median age: 66 years; range, 52–79) diagnosed with therapy-related AML (t-AML) or secondary AML who were enrolled in an Italian compassionate use program (across 31 centers; starting June 2018 and ending July 2019).[5]

At baseline, 50.2% of patients had secondary AML, 31% had t-AML, 18.8% had previous MDS-related changes and 24% had prior exposure to a hypomethylating agent.[5] More than half (56.3%) had abnormal cytogenetics and a high proportion (54.9%) had high European LeukemiaNet (ELN) 2017 risk scores.[5] In many cases, multiple comorbidities, including concomitant active neoplasm, would have precluded enrolment into a phase 3 trial.[5]

Median follow-up was 11 months (95% CI: 10.47–11.53) and the 12-month OS was 68.6% (median not reached; **Table 1**).[5] After first induction, overall remission (CR+CRi) was achieved in 64.8% of patients and the overall CR+CRi rate at the end of treatment was 70.4%.[5]

Table 1. Overall survival analysis (selected data only) from an Italian compassionate use program involving high-risk* AML patients treated with Vyxeos liposomal.[5]

Variable	Alive (%)	12-month OS (%)	Median OS	P-value (univariate)	P-value (mv)
Overall	50/71 (70.4)	68.6	NR	-	-
Age					
<70 years	38/51 (78.5)	73.0	NR	0.241	-
>70 years	12/20 (60.0)	58.3	NR		
Previous HMA					
No	38/54 (70.4)	68.9	NR	0.945	-
Yes	12/17 (70.6)	69.1	NR		
FLT3-ITD					
Negative	45/64 (70.3)	68.3	NR	0.570	-
Positive	3/5 (60.0)	60.0	NR		
TP53					
Wild type	20/24 (83.3)	83.1	NR	0.081	0.570
Mutated	7/13 (53.8)	51.9	NR		
ELN 2017 risk stratification					
Low/Int.	26/32 (88.9)	79.9	NR	0.073	0.071
High	24/39 (64.7)	59.5	NR		

ELN, European LeukemiaNet, HMA, hypomethylating agent; Int., intermediate; mv, multivariate; NR, not reached; OS, overall survival.
Adapted from: Guolo F, et al. Blood Cancer J. *2020;10(10):96.*

Among patients who achieved CR/CRi and had multiparameter flow cytometric (MFC)-minimal residual disease (MRD) analysis, 37.5% (15/40) tested negative, while 55.3% (21/38) of those evaluated with Wilms' tumor gene [WT1]-based MRD assessment tested negative.[5] A total of 40% (20/50) of patients achieving first CR underwent HSCT consolidation and had markedly lower annual relapse rates than non-transplanted patients (competing risk analysis: 5% vs 37.4%, respectively; P=0.012).[5] Although there was a trend towards reduced relapse risk observed for patients with MFC-MRD-negative CR, MRD-negativity did not result in better clinical outcome, possibly due to the small sample size.[5] Multivariate analysis confirmed that HSCT performed after achieving first CR was the only independent predictor of longer survival (P<0.05).[5]

In a separate landmark analysis, 12-month OS in patients receiving HSCT consolidation after achieving first CR was 100% compared with 70.5% in patients undergoing (or not) HSCT after first CR (P=0.011).[5] No transplant-related deaths were reported despite a high median age (65.5 years; range 54–73 years).[5]

Response rates were not affected by the presence of TP53 mutations, adverse risk profiles or unfavorable cytogenetics.[5] The CR/CRi rate for patients with or without TP53 mutations was 76.9% (10/13) and 75% (18/24), respectively (P=1.000), the CR/CRi rate for patients with low/intermediate vs high-risk* disease was 78.1% (25/32) and 64.1% (25/39), respectively (P=0.296), and the CR/CRi rate for patients with or without high-risk cytogenetic features was 59.4% (19/32) and 79.5% (31/39), respectively, (P=0.074).[5]

Most of the adverse events were infections, with a fever of unknown origin reported in 28% of patients, sepsis in 28% and pneumonia in 11.3%.[5] Patients receiving Vyxeos liposomal had prolonged neutrophil and platelet recovery, with a median time to absolute neutrophil count recovery (>0.5x10^9/L) of 38 days (range, 12–60) and a median time to platelet recovery (>25x10^9/L) of 28 days (range, 12–60).[5] Despite prolonged hematological recovery after Vyxeos liposomal induction, incidences of mucositis, severe infectious complications, and early mortality were lower than those observed after conventional intensive chemotherapy, and comparable to those observed in the pivotal phase 3 trial.[2,5] The 60 day treatment-related mortality rate was 7%.[5]

Based on these findings, the authors concluded that Vyxeos liposomal is an effective induction regimen for patients with high-risk* AML treated with curative aim, and may improve the results of HSCT through a reduction in treatment-related mortality and post-transplant relapse rate.[5] The authors also concluded that treatment with Vyxeos liposomal "can induce good quality remissions with acceptable toxicity in the majority of patients".[5]

Retrospective, multicenter cohort study in French clinical practice

To evaluate real-life experience with Vyxeos liposomal therapy, clinicians undertook a retrospective study of 103 adults with newly diagnosed, high-risk* AML treated with Vyxeos liposomal (between April 2018 and November 2019) according to the licensed posology across 12 centers in France.[6] The study cohort included a patient population with a broad age range of 20–83 years (median: 67 years), a high proportion had ELN 2017 adverse risk profiles (61%) and 18% had prior exposure to hypomethylating agents (HMAs) for treatment of myelodysplastic syndrome (MDS) and before progression to AML.[6] At study baseline, 72% of patients had AML-MRC and 26% had t-AML.[6]

The median OS was 16.1 months (range, 13.1–16.7) with a median follow-up of 8.6 months (range, 0.7–22.6).[6] The overall response rate (ORR: CR+CRi) after induction was 59% (**Table 2**).[6]

Table 2. Best response rates (selected data only) after Vyxeos liposomal induction in a cohort with high-risk* AML managed in French clinical practice.[6]

	CR/CRi, n (%)	P-value
All patients treated	61 (59)	
AML subtype		
t-AML	19 (70)	0.01
AML-MRC	40 (55)	
With/without prior MDS	15 (44)/46 (68)	0.14
With/without CMML	2 (22)/59 (63)	0.03
HMA exposure		
Prior HMA	4 (22)	0.001
No prior HMA	56 (69)	
ELN 2017 risk stratification		
Favorable	2 (100)	0.26
Intermediate	25 (66)	
Adverse	33 (54)	

AML, acute myeloid leukemia; AML-MRC, AML with myelodysplasia-related changes; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, complete response with incomplete neutrophil or platelet recovery; ELN, European LeukemiaNet; HMA, hypomethylating agent; MDS, myelodysplastic syndrome; t-AML, therapy-related AML.
Adapted from: Chiche E, et al. Blood Adv. *2021;5(1):176–184.*

Among patients who achieved CR or CRi, MRD was evaluable in 28 patients at the time of first consolidation cycle. Of these, 57% (16/28) reached a complete molecular response defined as an MRD $<10^{-3}$.[6] Over one-third (35%) of patients underwent allogeneic HSCT and achieved a significantly better median OS than non-transplanted patients (transplanted patients, median OS not reached vs non-transplanted patients, median OS 9.3 months [range, 4.4–14.2 months]; P<0.001).[6]

Following Vyxeos liposomal induction, data showed no statistically significant difference in overall response rates between FLT3-mutated and non-FLT3-mutated patients, and only the presence of mutated TP53 (P=0.02) or PTPN11 (P=0.004) predicted lower response in multivariate analyses.[6]

The results of this real-world study confirmed both the efficacy and acceptable safety profile of Vyxeos liposomal observed in the pivotal phase 3 trial. However, several adverse events not reported in the pivotal clinical trial were identified, including gastrointestinal toxicities (50%), cutaneous rash (25%) and alopecia (11%).[6] Median times to neutrophil recovery (>0.5x10^9/L) and platelet recovery (>20x10^9/L) after first induction were 29 days and 28 days, respectively.[6] Early mortality rates at Day 30 and 60 were 6% and 8%, respectively.[6] The mortality rate at Day 100 was 3% among patients that underwent HSCT.[6]

Conclusion

Clinical trial data, including long-term follow-up through 5 years and real-world evidence from multiple real-life clinic settings, suggest that Vyxeos liposomal treatment may lay the foundation for increased long-term survival prospects and durable remission in patients with newly diagnosed, high-risk* AML.[2,4–6]

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https://touchoncology.com/leukaemia/learning-zone/tfeat-treatment-high-risk-acute-aml/

*high-risk is defined as newly diagnosed, t-AML or AML-MRC.

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International Core Prescribing Information
Vyxeos® Liposomal 44mg/100mg powder for concentrate for solution for infusion (Daunorubicin and cytarabine)
Please refer to the Summary of Product Characteristics before prescribing.
Presentation: Purple lyophilised cake of powder for concentrate for solution for infusion. Each vial contains 44 mg of daunorubicin and 100 mg of cytarabine. After reconstitution the solution contains 2.2 mg/mL daunorubicin and 5 mg/mL cytarabine encapsulated in liposomes in a fixed combination in a 1:5 molar ratio. **Indication:** For the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC). **Dosage and administration:** For intravenous infusion use only. An in-line membrane filter may be used provided the minimum pore diameter of the filter is greater than or equal to 15 µm. It must not be administered via an intramuscular, intrathecal, or subcutaneous route. Refer to the full SmPC for detailed information on preparation of solution for infusion. Treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic medicinal products. Recommended dosing schedule for induction of remission: 44 mg/100 mg/m2, administered intravenously over 90 minutes on days 1, 3, and 5 as the first course of induction therapy; then on days 1 and 3 as subsequent course of induction therapy, if needed. Recommended dosing schedule for consolidation: The first consolidation cycle should be administered 5 to 8 weeks after the start of the last induction. The recommended dosing schedule is 29 mg/65 mg/m2, administered intravenously over 90 minutes on days 1 and 3 as subsequent courses of consolidation therapy, if needed. Dose adjustments during treatment may be required in hypersensitivity symptoms and cardiotoxicity. Assessment of cardiac function prior to start of treatment is recommended. Renal impairment: Dose adjustment is not required for patients with mild (creatinine clearance [CrCL] 60 mL/min to 89 mL/min by Cockcroft Gault equation [C-G]) or moderate (CrCL 30 mL/min to 59 mL/min) renal impairment. There is no experience in patients with severe renal impairment (CrCL 15 mL/min to 29 mL/min) or end-stage renal disease. It should only be used in patients with severe renal impairment if the benefits outweigh the risks. Hepatic impairment: Dose adjustment is not required for patients with a bilirubin level less than or equal to 50 µmol/L. There is no experience in patients with hepatic impairment resulting in a bilirubin level greater than 50 µmol/L. It should only be used in patients with severe hepatic impairment if the benefits outweigh the risks. Elderly population (≥65 years): No dose adjustment is required. Paediatric population: The safety and efficacy in children aged 0–18 years has not yet been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings, precautions and interactions:** Do not substitute or interchange with other daunorubicin and/or cytarabine-containing products. Severe myelosuppression and serious or fatal haemorrhagic events have been reported. Due to the long plasma half-life of Vyxeos Liposomal, time to recovery of ANC and platelets may be prolonged and require additional monitoring. Prophylactic anti-infectives may be administered during the period of profound neutropenia until ANC returns to 500/µL or greater. If myelosuppressive complications occur, appropriate supportive measures should be used. Blood counts should be regularly monitored until recovery. As cardiotoxicity is a known risk prior therapy with anthracyclines, pre-existing cardiac disease, previous radiotherapy of the mediastinum, or concomitant use of cardiotoxic products may increase the risk. Hepatotoxic medicinal products may impair liver function and increase toxicity. Evaluation of hepatic and renal function is recommended prior to administration and periodically during treatment. Blood uric acid levels should be monitored and appropriate therapy initiated if hyperuricemia develops. Each vial of Vyxeos Liposomal contains 100 mg of copper gluconate. It should only be used in patients with a history of Wilson's disease or other copper-related disorder if the benefits outweigh the risks. To avoid local tissue necrosis care should be taken to ensure that there is no extravasation of Vyxeos Liposomal during administration. Administration of live or live-attenuated vaccines should be avoided. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished. The absorption of oral accompanying medicinal products may be considerably influenced by gastrointestinal mucositis and/or diarrhoea frequently occurring in association with intensive chemotherapy. **Pregnancy, lactation and fertility:** There are no data on use in pregnant women. It should not be used during pregnancy unless the benefit of treatment outweighs the risk. It is not known if Vyxeos Liposomal is excreted in human milk therefore mothers should be advised to discontinue breastfeeding during therapy. Patients should be advised to avoid becoming pregnant while receiving Vyxeos Liposomal. Male patients and women of childbearing potential must use an effective method of contraception during treatment and for 6 months following the last dose. Male fertility may be compromised by treatment. **Undesirable effects: Please refer to the full SmPC for the complete list of undesirable effects.** The most frequently occurring adverse reactions were hypersensitivity, febrile neutropenia, oedema, diarrhoea/colitis, mucositis, fatigue, musculoskeletal pain, abdominal pain, decreased appetite, cough, headache, chills, arrhythmia, pyrexia, sleep disorders, and hypotension. The most serious and frequently occurring ADRs were infection, cardiotoxicity and haemorrhage. **Overdose:** There is no specific antidote for overdose and treatment should be symptomatic. **Storage and Handling:** Store in a refrigerator (2°C - 8°C). Shelf life of unopened vials: 2 years. Keep vial in the original carton to protect from light and store in an upright position. Vyxeos Liposomal is a cytotoxic medicinal product intended for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents. **Legal category:** POM. **Marketing authorisation number:** EU/1/18/1308/001. **Package quantity and Cost:** carton containing 1 × 50 mL vial. Price differs across countries. Further information is available from the **Marketing Authorisation Holder:** Jazz Pharmaceuticals Ireland Ltd., 5th Floor, Waterloo Exchange, Waterloo Road, Dublin D04 E5W7, Ireland. **Date of preparation:** November 2019. **Job Code:** INT-VYX-1900009.
Vyxeos® is a registered trade mark.
For country specific information please refer to your local SmPC or Product Monograph

Adverse events should be reported. Healthcare professionals are asked to report any suspected adverse events via their national reporting system. Adverse events should also be reported to Jazz Pharmaceuticals by email to **aereporting@jazzpharma.com**

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