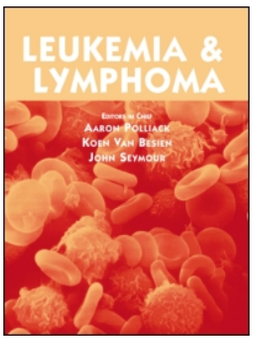

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LETTER TO THE EDITOR



# Frequency of infusion-related reactions with CPX-351 treatment in an observational study in adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes (AML-MRC)

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Infusion-related reactions are common during or after the administration of liposomal drugs. For example, up to 10% of patients treated with Doxil® (pegylated liposomal doxorubicin) experience acute infusion-related reactions, including flushing, dyspnea, facial swelling, headache, chills, back pain, chest or throat tightness, and/or hypotension, and some serious, life-threatening allergic/anaphylactoid-like infusion-related reactions have been reported [1]. Furthermore, across multiple studies, up to 24% of patients treated with AmBisome® (liposomal amphotericin B) experienced infusion-related reactions, including vomiting, nausea, fever, chills, respiratory events, hypotension, hypertension, tachycardia, vasodilation, dyspnea, hyperventilation, and hypoxia [2]. However, the design of each liposomal agent is different, leading to a large variation in the frequency and severity of infusion-related reactions.

CPX-351 (United States: Vyxeos®; Europe: Vyxeos® Liposomal), the first dual-drug liposome, encapsulates daunorubicin and cytarabine in a synergistic 1:5 molar ratio [3–6]. CPX-351 is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) [7,8]. The pivotal phase 3 study that supported these approvals evaluated CPX-351 versus the conventional 7 + 3 regimen of cytarabine and daunorubicin in older adults with newly diagnosed high-risk/secondary AML. After a median follow-up of 20.7 months, induction followed by consolidation with CPX-351 significantly improved median overall survival versus 7 + 3 (9.56 vs 5.95 months; hazard ratio = 0.69 [95% confidence interval: 0.52, 0.90]; 1-sided $p = 0.003$) [9], and this survival benefit was maintained in a long-term 5-year follow-up analysis (hazard ratio = 0.70 [95% confidence interval: 0.55, 0.91]) [10]. The safety profile of CPX-351 was generally consistent with the known safety profile of 7 + 3 [9].

Intensive monitoring for infusion-related reactions with CPX-351 administration had not previously been reported. This postmarketing, observational, single-arm, multicenter study (NCT03526926) was requested by the FDA to assess the nature, incidence, and severity of infusion-related reactions during an initial CPX-351 induction. All patients provided informed consent, and the study was approved by institutional review boards at each participating center. Prior to enrollment, the treating investigator decided to prescribe CPX-351 based on the approved US indications [8]. Eligible patients were adults aged ≥18 years with newly diagnosed t-AML or AML-MRC. Patients who previously received CPX-351 or any investigational agent were ineligible. Patients could receive up to 2 inductions with CPX-351 at the US label dosage (daunorubicin 44 mg/m$^2$ and cytarabine 100 mg/m$^2$) by 90-minute infusion on Days 1, 3, and 5 (Days 1 and 3 for second induction) and up to 2 consolidations with CPX-351 (daunorubicin 29 mg/m$^2$ and cytarabine 65 mg/m$^2$) by 90-minute infusion on Days 1 and 3. Patients who developed a hypersensitivity reaction received premedication at all subsequent infusions. Patients could receive antiemetic and antihyperuricemic agents according to each site's standard institutional practice.

Patients were observed for the first 6 days of the first CPX-351 induction cycle, from Day 1 of treatment until 1 day after the last infusion (Day 6), although patients

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**Table 1.** Exposure to CPX-351.

| *n* (%) | CPX-351 ($N = 52$) |
|---|---|
| Number of infusions | |
| Patients received ≥1 infusion | 52 (100) |
| Patients received 1 infusion | 1 (2) |
| Patients received 2 infusions | 2 (4) |
| Patients received 3 infusions | 49 (94) |
| Number of infusions/patient | |
| Mean (SD) | 2.9 (0.3) |
| Median (range) | 3.0 (1, 3) |
| Patients with dose interruptions during the treatment period | 1 (2) |
| Patients with dose interruptions on Day 1 of infusion | 1 (2) |
| Patients with dose interruptions on Day 3 of infusion | 0 |
| Patients with dose interruptions on Day 5 of infusion | 0 |
| Cumulative dose of daunorubicin, mg | |
| Mean (SD) | 238.2 (53.8) |
| Median (range) | 247.5 (88, 339) |
| Cumulative dose of cytarabine, mg | |
| Mean (SD) | 542.4 (122.6) |
| Median (range) | 562.5 (204, 774) |

SD: standard deviation.

may have received subsequent treatment at their physician's discretion. The incidence and severity of infusion-related reactions were evaluated during and for 90 minutes after the completion of each CPX-351 infusion. Treatment-emergent adverse events (TEAEs) were collected throughout the 6-day observation period and were graded according to the NCI-CTCAE version 4.03. TEAEs were followed until resolution, stabilization, or permanent sequelae were identified, or until the patient was lost to follow-up.

A total of 52 patients were enrolled in the study and received ≥1 CPX-351 induction. The median age was 64 years (range: 28, 78), with 67% of patients aged ≥60 years; 56% were male; 79% were White; and 23%, 46%, and 23% had Eastern Cooperative Oncology Group performance scores of 0, 1, and 2, respectively. Most patients had no history of allergies (63%), allergic asthma (98%), or autoimmune disorders (87%).

Most (94%) patients received all 3 infusions of the first CPX-351 induction (Table 1). Three patients discontinued the study. One patient developed a serious event of thromboembolism after receiving 2 CPX-351 doses and subsequently died. Another patient discontinued at their physician's discretion on Day 6 after receiving 2 CPX-351 doses due to a general decline with multiple adverse events that were not improving; the patient subsequently died on Day 10. Events for both patients were considered unrelated to CPX-351 by the investigators. The third patient discontinued on Day 2 after 1 CPX-351 dose due to tenuous health status and inability of the infusion center to collect study-mandated vital signs; this patient experienced grade 2 pyrexia (considered related to CPX-351) and grade 3 dyspnea (considered unrelated to CPX-351).

One (2%) patient experienced infusion-related reactions during the study. This patient was a 68-year-old White male with AML evolving from prior myelodysplastic syndromes and no known history of asthma, allergies, or autoimmune diseases. He experienced grade 1 pyrexia on Day 2 (~24 to 25 h after the first infusion on Day 1) and grade 2 dyspnea on Day 4 (~21 h after the second infusion on Day 3). Both reactions were continuing at the end of the study (Day 6) but did not lead to dose change or interruption, treatment discontinuation, or withdrawal from the study.

In total, 39 (75%) patients experienced any grade TEAEs (including infusion-related reactions), and 13 (25%) patients experienced grade 3 or 4 TEAEs within the 6-day observation period (Table 2). Serious TEAEs were experienced by 6 (12%) patients and included grade 4 respiratory failure ($n = 2$ [4%]), grade 2 pyrexia, grade 3 dyspnea, grade 3 tumor lysis syndrome, grade 3 lung infection, grade 5 sepsis, grade 5 thromboembolism, and grade 5 cerebrovascular accident ($n = 1$ [2%] each). Of the serious TEAEs, only pyrexia and tumor lysis syndrome were considered related to CPX-351 by the investigator. Serious TEAEs of pyrexia, dyspnea, and tumor lysis syndrome resolved by Day 2, Day 3, and Day 12, respectively; although the lung infection was resolving, the patient died on Day 6 due to hemorrhagic stroke. Neither of the serious TEAEs of respiratory failure resolved; 1 of these patients also experienced a serious TEAE of sepsis that resulted in death. The serious TEAEs of thromboembolism and cerebrovascular accident also resulted in patient death. None of the 3 deaths due to serious TEAEs were considered related to CPX-351 by the investigator.

In this postmarketing, observational study in adults with newly diagnosed t-AML or AML-MRC, the frequency of infusion-related reactions with CPX-351 was low. No infusion-related reactions occurred on Day 1 of the first induction course of CPX-351. Among 52 patients, only 1 experienced infusion-related reactions, both of which were grade 1 to 2 and did not lead to study discontinuation. Similar rates of infusion-related reactions with CPX-351 treatment have been observed in other clinical studies; however, these studies were not designed to evaluate infusion-related reactions. In the pivotal phase 3

**Table 2.** Summary of TEAEs[a] in all patients who received CPX-351.

| *n* (%) | CPX-351 (*N* = 52) |
|---|---|
| Any TEAE[b] | 39 (75) |
| Constipation | 9 (17) |
| Fatigue | 7 (13) |
| Pneumonia | 7 (13) |
| Peripheral edema | 6 (12) |
| Headache | 6 (12) |
| Any grade 3 or 4 TEAE[c] | 13 (25) |
| Anemia | 3 (6) |
| Thrombocytopenia | 2 (4) |
| White blood cell count decreased | 2 (4) |
| Respiratory failure | 2 (4) |
| Any serious TEAE | 6 (12) |
| Respiratory failure | 2 (4) |
| Pyrexia | 1 (2) |
| Lung infection | 1 (2) |
| Sepsis | 1 (2) |
| Tumor lysis syndrome | 1 (2) |
| Cerebrovascular accident | 1 (2) |
| Thromboembolism | 1 (2) |
| Dyspnea | 1 (2) |
| Interruption due to TEAE | 1 (2) |
| Discontinuation due to TEAE | 0 |
| Death due to TEAE | 3 (6) |

TEAE: treatment-emergent adverse event.
[a]TEAEs reported during the 6-day study period from the start of the first CPX-351 infusion on Day 1 through 1 day after the last infusion (Day 6).
[b]Subsequent list includes all individual TEAEs reported in >10% of patients.
[c]Subsequent list includes all individual grade 3 or 4 TEAEs reported in >1 patient.

study, 2 of 153 (1%) patients in the CPX-351 arm experienced grade 2 infusion-related reactions, which was similar to the 7 + 3 comparator arm (2 of 151 [1%] patients with grade 1 or 2 reactions; data on file). In a phase 2 study of CPX-351 in newly diagnosed *de novo* or secondary AML, 1 of 85 (1%) patients had an infusion-related reaction (data on file). In a CPX-351 US early access program in patients with newly diagnosed high-risk/secondary AML, 1 of 52 (2%) patients experienced an infusion-related reaction (data on file).

Liposomal-based agents are known to induce infusion-related reactions, but the molecular basis of these reactions is not fully understood [11]. Nanomedicine physiochemical properties associated with infusion-related reactions include surface charge, homogeneity, particle size, presence of lipids, and presence of cholesterol in the bilayer or as crystal on the surface [11]. The composition and structure of the CPX-351 liposome are unique from prior liposomal products and may decrease the risk for infusion-related reactions following CPX-351 administration. CPX-351, the first dual-drug liposome, was developed using the CombiPlex platform and contains liposome bilayers of distearoylphosphatidylcholine, distearoylphosphatidylglycerol, and cholesterol at a 7:2:1 molar ratio [12]. This structure results in both a high liposomal melting point, allowing CPX-351 to remain in the gel phase at body temperature, and stabilization of hydrophilicity and the lipid bilayer [12]. This stability results in limited systemic distribution and allows for the preferential uptake of CPX-351 by leukemic cells [4,6,12]. Furthermore, while most single-agent liposomes incorporate polyethylene glycol (PEG)–modified lipids, CPX-351 instead contains anionic phosphatidylglycerol as a stabilizing phospholipid, thereby forgoing immune system recognition of PEG and eliminating the likelihood of PEG-related reactions [12].

The reported TEAEs and serious TEAEs in this study were consistent with the safety profile previously reported for CPX-351 in other clinical studies [9,13–15]. A total of 39 (75%) patients experienced any grade TEAEs, 13 (25%) patients experienced grade 3 or 4 TEAEs, and 6 (12%) patients experienced serious TEAEs; no TEAE led to study discontinuation. Three deaths were reported during the study, none of which were considered related to CPX-351 by the investigator.

Taken together, these data support the prior safety profile reported in the pivotal phase 3 study [9], with no new safety signals identified.

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## Disclosure statement

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## Data availability statement

All relevant data are provided within the manuscript and supporting files.

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