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CASE REPORT

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CPX-351 (Vyxeos®) can cause severe rash in acute myeloid leukemia—A case report

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Abstract

CPX-351, a promising new agent for patients with treatment-related and secondary acute myeloid leukemia can lead to a severe whole-body rash. Although severe side effects are rare, treatment should be carefully monitored at specialized centers.

KEYWORDS

acute myeloid leukemia, CPX-351, elderly, rash

1 | INTRODUCTION

Acute myeloid leukemia (AML) is a hematologic neoplasm resulting in a disturbed regeneration of blood cells. Due to heterogeneous genetic mutations in AML, different subgroups are classified.[1] Approximately 25% of all AML cases correspond to the group of secondary AML, and are associated with a worse overall outcome.[2] This group includes AMLs with prior myeloid diseases and AML with myelodysplasia-related changes (AML-MRC). A promising therapy for older patients with AML-MRC has recently been introduced and licensed by FDA and EMA: CPX-351 (Vyxeos®).

In a phase III trial CPX-351, a liposomal formulation of cytarabine and daunorubicin was superior to the standard 7 + 3 induction therapy (7 days cytarabine, 3 days anthracycline therapy) in median overall survival and overall remission rates.[3] Patients ≥65 years especially benefited from the therapy as the death rate was 12.3% in the CPX-351 group vs 23.1% in the control group.[4] The safety profile of CPX-351 and the common 7 + 3 regimen was comparable. The most frequent adverse events were febrile neutropenia, fatigue, pneumonia, hypoxia, hypertension, bacteremia, and sepsis.[3] According to the EMA assessment report skin reactions occurred in 39.2% in the CPX-351 group vs 25% in the 7 + 3 regimen.[4] The clinical phase III study that leads to EMA and FDA approval showed severe skin reactions (> grade 3) in eight patients (5%) in the vyxeos group vs two patients (1%) in the 7 + 3 group.[5]

Ruth M. Urbantat and Valentin Popper contributed equally to this work.

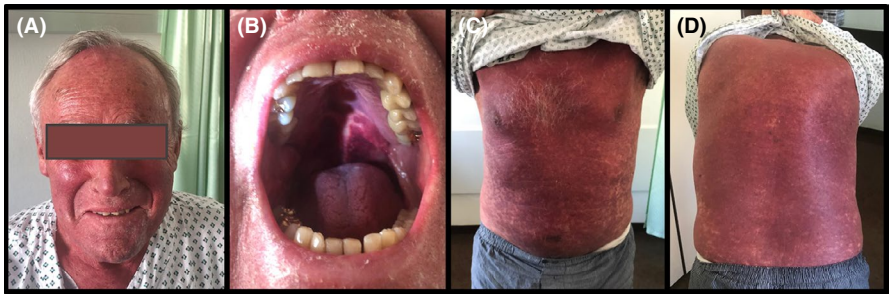

FIGURE 1 Clinical manifestation of the rash. Clinical manifestation of the maculopapular rash with subcutaneous hemorrhage after 2 wk. A showing the patient's face. B showing the patient's oral mucosa. C and D showing the patient's torso

This case report describes a severe whole-body exanthema as a side effect of CPX-351 during the induction phase of AML treatment.

2 | CASE PRESENTATION

A 74-year-old man was admitted to the hematology-oncology department to further evaluate his newly diagnosed AML. The patient had noticed a husky voice over the course of 2 months prior to diagnosis. In addition, he reported the recent occurrence of insomnia and night sweats but no fever or weight loss. In the physical examination, the skin was intact, there were no signs of internal or external bleeding and no palpable lymph nodes or other abnormalities.

Routine blood tests showed a pancytopenia (erythrocytes 3.9/pL, Hb 13.5 g/dL, thrombocytes 147×10^9/L, leucocytes 1.8×10^9/L). Apart from a slightly reduced GFR (64 mL/min) all other laboratory results were normal. Tests for cytomegaly virus, hepatitis, and HIV-infections came back negative. We then conducted a chest x-ray, spirometry as well as an ECG and echocardiography. All tests were unremarkable and appropriate for his age.

The bone marrow biopsy showed a secondary AML subtype M2[6] with MDS-like changes and multilineage dysplasia. As screening for genetic markers only later on revealed a NPM1A mutation the patient was initially diagnosed with AML-MRC. DNMT3A and ASXL1 were mutant as well whereas he carried the FLT3 wild-type variant. Furthermore, cytogenetic analysis showed a normal karyotype. Several clinical scores were applied, namely the ECOG,[7] HCT-CI,[8] and the Charlson-score.[9] Our patient scored 0 points in every single one of them and did not provide any comorbidities apart from hyperlipidemia as well as hypothyroidism. Taking into consideration all previously mentioned risk factors we categorized him as a low-risk patient according to European LeukemiaNet (ELN)[10] and started induction phase with CPX-351. To prevent unwanted side effects, we administered folic acid as well as an antibiotic (trimethoprim/sulfametrol, TMP-SMX) and antimycotic (posaconazole) medication. During the induction phase, the patient also received substitution therapy for his hypothyroidism and trazodone for the recently occurring insomnia.

Ten days after the initial dose of Vyxeos®, he developed a non-itchy papular rash on the back of his neck. After an episode of shivers and epistaxis, we commenced with an empiric intravenous antibiotic therapy consisting of piperacillin/tazobactam. The thrombocytopenia and anemia were monitored frequently and treated with transfusion of thrombocytes (13 concentrates) and erythrocytes (four concentrates) over the course of several weeks. Due to the papular exanthema worsening and the patient has developed a fever, the antibiotics were changed to meropenem and vancomycin. As there was no focus on infection and serum levels of c-reactive-protein (CRP) were in normal range, we escalated the antibiotic, antimycotic, and antiviral therapy to shield the patient from all potential infections.

While the rash still worsened and spread over the whole body, even to the oral and nasal mucosa (see Figure 1), the patient never reported any itchiness or pain. Furthermore, the rash changed from papular to maculopapular and developed a dark red, almost violet color due to subcutaneous hemorrhage. The rash was treated with a high-dose intravenous glucocorticoid and desloratadine as well as topic therapy consisting of lauromacrogol 400 (thesit®), chlorhexidine, and betamethasone-cream (diproderm) and later tannosynt® compresses.

We evaluated the rash every other day with a dermatology consultant. Five days after the rash had spread over the whole body, the patient's skin turned brownish and started to peel off. The patient did not give consent to a skin biopsy. Over the course of another 2 weeks, the rash slowly resolved. At the same time, blood counts were recovering. Thirty-five days after the induction, we re-biopsied his bone marrow to assess the treatment effect. Cytomorphology (<1% blasts), histological evaluations as well as the NGS (NPM1, DNTM3A negative) screening for genetic markers showed complete (molecular) remission. Due to his stable clinical condition, we deescalated the anti-infective therapy and slowly reduced the glucocorticoids before discharging the patient from the hospital.

3 | DISCUSSION

Here we report a severe rash as an adverse event during treatment for AML with CPX-351. Our initial suspicion was that the rash occurred as a combined reaction to

immunosuppression and the treatment with piperacillin/tazobactam. However, the rash worsened after the antibiotics were discontinued. It is highly unlikely that piperacillin/tazobactam was the triggering agent because this type of rash is generally self-limiting and usually resolves within days upon discontinuation of the drug. Our patient's rash, however, took more than a week to resolve after reaching its climax at day 17 (piperacillin/tazobactam was applied on days 3-5). In addition to that, the application of the Naranjo probability scale[11] established a probable association between CPX-351 and the rash.

Additionally, TMP-SMX was taken into consideration as the triggering agent. TMP-SMX is known to cause skin reactions in 2%-4% of patients.[12,13] These skin reactions range from isolated maculopapular eruptions to Stevens-Johnson syndrome and toxic epidermal necrolysis.[12,14,15] A study by Jick et al[12] reported that 50% of rashes occurred within 72 h upon introduction of TMP-SMX. Although discontinuing TMP-SMX was discussed within the team we decided against it. TMP-SMX was administered again during consolidation therapy not leading to a skin eruption or other adverse reactions. Thus, it is unlikely that TMP-SMX was the cause of our patient's whole-body exanthema.

Cytarabine and daunorubicin are the individual components of CPX-351. Cutaneous toxicity of cytarabine has been described in several studies.[16-19] A prospective report of 118 patients by Cetkovska et al[16] found that half the patients receiving high-dose cytarabine therapy suffered from dermal eruptions. A similar-looking, yet less severe rash was reported in 2013 in a male patient with relapsed AML during high-dose cytarabine therapy.[20] Daunorubicin and other liposomal formulated anthracyclines like doxorubicin have long been known for their skin toxicity[21] causing various skin eruptions, for example, hand-foot syndrome,[22] diffuse follicular rash, and intertrigo-like eruptions.[23] CPX-351 has a distinct prolonged half-life compared with cytarabine and daunorubicin.[24,25] Furthermore, cytarabine is mainly excreted in the urine. Although no dose adjustment is recommended for patients with mild renal impairment during therapy with CPX-351, it is possible that it led to an increase of exposure of cytarabine in our patient.[5] Moreover, keratinocytes have a rapid turnover rate which makes them more susceptible for cytotoxic damage induced by chemotherapy.[26] We believe that a combination of prolonged local effects of the liposomal formulation of cytarabine and daunorubicin on the epidermis through anthracycline related upregulation of cytotoxic receptor CD95 and TNFαR[27,28] and the production of free radicals in the immuno-compromised patient could have led to the rash.

Although developing a rash has been described as a frequent side effect during and after treatment with CPX-351 only a low percentage of patients develop a severe rash (4.3%-5%).[4,5] In addition to that, the EMA assessment report showed that patients undergoing therapy with CPX-351 are more likely to develop a rash classified as a Grade 3 or higher treatment-emergent adverse event than patients of the 7 + 3 group.[4] To date, only a few cases with severe rash have been reported to the manufacturer. However, none of them have been published in detail. As described before, a rash is more likely to appear during induction rather than the consolidation phase which is consistent with our patient's symptoms during induction phase.[4] The choice of CPX-351 for induction treatment in our patient was based on the promising results from the recently published phase III trial leading to licensing in Europe and the US.[5] There, patients receiving CPX-351 had a better median overall survival (OS) compared with the standard 7 + 3 regimen (9.56 vs 5.95 months).[5] Complete remission (CR) rates were also significantly improved by CPX-351 (37.3% vs 25.6% with 7 + 3). Finally, this decision was justified by taking the patient's clinical condition, comorbidities, and physical fitness into consideration.[29] CR was achieved after one cycle of CPX-351. For subsequent consolidation therapy, intermediate-dose cytarabine was chosen to reduce the risk for a reoccurring rash resulting in ongoing CR. Under the consolidation therapy, the patient did not develop a rash. Furthermore, we registered the patient for an allogenic stem cell transplantation (SCT). The final decision on the therapy had not been made at the point of publication as the patient was still evaluating his options.

4 | CONCLUSIONS

In our experience CPX-351 can lead to a severe life-threatening exanthema during induction phase treatment of AML. However, CPX-351 is an effective approach in the treatment of elderly patients with secondary AML and severe skin reactions are rare and manageable as shown by our case report. The patient should be monitored carefully in a specialized care unit during and after treatment with CPX-351. Using CPX-351 may be considered safe while bearing in mind its potential severe side effects.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

RMU and VP: contributed equally. All authors were involved in the clinical management of the patient. RMU and VP:

reviewed the literature and drafted the manuscript. All authors contributed to the writing and approved the final manuscript.

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