Title: CPX-351 (Vyxeos®) can cause severe rash in acute myeloid leukaemia – a case report

Running head: CPX-351 can cause severe rash in AML

Key words: AML, elderly, rash, CPX-351

Key clinical message:

CPX-351 is a promising new agent for patients with treatment related and secondary acute myeloid leukemia. Because of potential severe side effects treatment should be carefully monitored at specialized centers.

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Introduction

Acute myeloid leukaemia (AML) is a hematologic neoplasm resulting in a disturbed regeneration of blood cells. Due to heterogenous genetic mutations in AML, different subgroups are classified1. 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 classic 7+3 induction therapy (7 days cytarabine, 3 days anthracycline therapy) in median overall survival and overall remission rates3. Especially patients ≥ 65years 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 is comparable. Most frequent adverse events were febrile neutropenia, fatigue, pneumonia, hypoxia, hypertension, bacteraemia and sepsis 3. According to EMA 4 skin reactions occurred in 39.2% in the CPX-351 group vs 25% in the 7+3 regimen.
This case report describes a severe whole-body exanthema as a side effect of the therapy with CPX-351 during induction phase of AML.

Case presentation

A 74-year-old male was admitted to the haematology-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 to that, he reported the recent occurrence of insomnia, night sweats, however no fever or weight loss. In the physical examination the skin was intact, there were no signs of internal or external bleeding, no palpable lymph nodes or other abnormalities.
Routine blood tests showed a pancytopenia with (Hb 13.5g/dl, thrombocytes 147×109/l, leucocytes 1.8×109/l). Apart from a slightly reduced GFR (64ml/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, M2 5 after myelodysplastic syndrome with multilineage dysplasia (MDS-MLD). To further asses the patient´s risk factors and therapeutic options we screened for genetic markers and comorbidities. NPM1A, DNMT3A and ASXL1 were mutant whereas he expressed the FLT3 wildtype variant. Furthermore, cytogenetic analysis showed a normal karyotype. Several clinical scores were applied, namely the ECOG 6, HCT-CI 7 and the Charlson-score 8. Our patient scored 0 points in every single one of them and did not provide any comorbidities apart from hyperlipidaemia as well as hypothyroidism. Taking in consideration all previously mentioned risk factors we categorized him as a low risk patient according to European LeukemiaNet (ELN)9 and started induction phase with CPX-351. To prevent unwanted side effects, we administered folic acid as well as an antibiotic (sulfametrol/trimethoprim) and antimycotic (posaconazole) medication. During the induction phase the patient also received substitution therapy for his hypothyroidism and trazodone for recently occurred insomnia.

10 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 anaemia were monitored frequently and treated with transfusion of thrombocytes (13 concentrates) and erythrocytes (4 concentrates) over the course of several weeks. As the papular exanthema aggravated and the patient developed fever, antibiotics were changed to meropenem and vancomycin. As there was no focus of 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 and 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 colour due to subcutaneous haemorrhage. The rash was treated with a high dose intravenous glucocorticoid and desloratadine as well as topic therapy consisting of lauromacrogol 400 (thesit®), chlorhexidine and betamethasonecream (diproderm) and later tannosynt® compresses.

We evaluated the rash every other day with dermatology consultant. 5 days after the

rash had spread over the whole body, the patient´s skin turned brownish and started to peel off. We refrained from a skin biopsy due to low platelet levels and neutropenia. Over the course of another 2 weeks the rash slowly resolved. At the same time blood counts were recovering. 35 days after 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.

Discussion

Here we report a severe rash as adverse event during treatment for AML with CPX-351. Although severe rash has been described and is a frequent side effect during and after treatment with CPX-351, to date only a few cases with severe rash have been reported to the manufacturer. However, none of them has been published in detail. As described before a rash is more likely to appear during induction rather than consolidation which confides with our patient´s symptoms during induction phase.

Our initial suspicion was that the rash occurred as a combined reaction to immunosuppression and the treatment with piperacillin/tazobactam. However, the rash aggravated after the antibiotics were discontinued which is highly unlikely with piperacillin/tazobactam as the triggering agent where the 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 scale 10 established a probable association between CPX-351 and the rash.

Cytarabine has not been described to lead to any kind of skin eruption. However, other liposomal formulated anthracyclines like doxorubicin have long been known for their skin toxicity 11. Keratinocytes have a rapid turnover rate which makes them more susceptible for cytotoxic damage induced by chemotherapy.12 A combination of prolonged local effects of CPX-351 on the epidermis through anthracycline related

upregulation of cytotoxic receptor CD95 and TNFαR13,14 and the production of free radicals in the immuno-compromised patient could have led to the rash.
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. There, patients receiving CPX-351 had a better median overall survival (OS) compared to the standard 7+3 regimen (9.56vs 5.95 months)3. Complete remission (CR) rates were also significantly improved by CPX-351 (37.3% vs 25.6% with 7+3). Furthermore, results for the subgroup of patients with MDS karyotype (46.3% vs 27.0% with 7+3 suggested a potential benefit for our specific patient 3. Finally this decision was justified by taking the patient´s clinical condition, comorbidities and physical fitness into consideration15. CR was achieved after one cycle of CPX-351. For subsequent consolidation therapy intermediate dose ARAC was chosen to reduce the risk for a reoccurring rash resulting in ongoing CR. 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.

Conclusions

In our experience CPX-351 can lead to 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 the risk for severe skin reactions should not preclude its use. These skin reactions are presumably rare (this is the first report) and manageable as shown by our case report. Using CPX-351 may be considered safe while bearing in mind its potential severe side effects. During and after treatment with CPX-351 the patient should be monitored carefully in a specialised care unit.

Consent for publication: written informed consent was obtained from the patient

Competing interests: The authors declare that they have no competing interests.

Conflict of interest:

None declared.

Authors‘contributions:

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.