

Case Report,

## A Favorable Outcome With CPX-351 Liposome (Vyxeos) in the Management of A Sporadic Monosomy 7 Myelodysplastic Syndrome Related Acute Myeloid Leukemia

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### Abstract:

**Introduction:** Although Acute Myeloid Leukemia (AML) has been associated with several environmental factors, in some patients the evolution to AML is preceded by myelodysplastic syndrome (MDS). We report a case of 63-year-old male who was diagnosed with sporadic monosomy 7 MDS/AML who achieved good response to treatment with CPX-351 (Vyxeos) induction chemotherapy.

**Case information:** A 63-year-old male initially presented to the ED for further evaluation of pancytopenia that was discovered incidentally during a routine office visit. Further evaluation revealed his blast count was elevated with presence of Auer rods, myelocytes and basophilia. He was admitted for further work-up of pancytopenia with suspicion being for MDS/AML and bone marrow biopsy for flow cytometric evaluation of the bone marrow was strongly suggestive of acute myeloid leukemia, with morphology suggesting a predisposing MDS. Subsequent molecular cytogenetic [FISH] report confirmed -7/7q abnormality in 80% of nuclei with loss of 1 copy of chromosome 7. The following week, patient was initiated on CPX-351 [Vyxeos; daunorubicin and cytarabine liposome for injection]. Bone marrow biopsy following induction chemotherapy showed 11 to 12% of CD34 positive myeloid blasts with abnormal myeloid maturation, representing notable improvement with greater than 50% reduction in his blast count.

**Conclusion:** Sporadic monosomy 7 MDS/AML that arises without evidence of germline genetic predisposition and in the absence of other predisposing medical conditions or treatments is an uncommon subset of AML. Vyxeos induction chemotherapy may be an excellent option in the management of sporadic monosomy 7 MDS/AML.

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**Keywords:** case report, hematologic malignancy, acute myeloid leukemia, CPX-351 (Vyxeos), monosomy 7, myelodysplastic syndrome, induction chemotherapy, cytarabine/daunorubicin

### Introduction:

Acute myeloid leukemia (AML) is a heterogeneous group of cancers that arise from the clonal expansion of malignant hematopoietic precursor cells. In some patients the evolution to AML is preceded by myelodysplastic syndrome (MDS), a form of secondary AML. Most of such newly diagnosed patients are managed with a combination regimen of cytarabine plus

daunorubicin (7+3 most commonly), and this poses a significant problem for multiple subsegments within AML, such as patients with specific molecular aberrations <sup>[1]</sup>. Of note, the presence of a single monosomy (excluding loss of a sex chromosome) is associated with a negative outcome <sup>[2]</sup>. CXP-351 liposome injections (Vyxeos) has been shown to improve complete remission rates and overall survival compared to

standard 7+3 regimen of cytarabine and daunorubicin in specific patient populations [3]. We report a case of a patient with sporadic monosomy 7 related MDS progressing to secondary AML who achieved good response rates to CPX-351 liposome chemoinduction.

### **Case report:**

A 60-year-old male with a past medical history for hypertension presented to the emergency department for further evaluation of dyspnea on exertion and dizziness worsening with positional changes. He denied orthopnea/PND. He also noted an insect bite on the external side of his left ankle the day before presentation, following which the patient noted that he soaked his socks from the bleeding, and it subsequently resolved with compression. He denied a history of recent infections or fevers. He has not been diagnosed with malignancies in the past and has not received radiotherapy/chemotherapy treatments. He denied known family history of hematologic malignancy. He had sought cardiology evaluation prior to this presentation for the same symptoms, and had undergone a stress test that was nonischemic, and was noted to have a coronary calcium score of 0. Echocardiogram showed normal left ventricular size and systolic function with only mild aortic regurgitation. He takes enalapril 20 mg twice daily, labetalol 200 mg twice daily and amlodipine 5 mg daily for management of hypertension. Dose adjustment of these medications did not alter his symptomatology.

Physical examination revealed a well-nourished male in no acute distress with scattered bruises noted on his extremities and a 1 cm clean abrasion over the left lateral ankle without bleeding stigmata. System examination was otherwise unremarkable.

Initial lab work was significant for a complete blood count [CBC] which showed a white blood cell [WBC] of  $2.8 \times 10^9/L$ , hemoglobin of 6.5 g/dL, and platelet count of  $47 \times 10^9/L$ . Of particular note, a CBC done two months ago demonstrated a WBC count of  $3.5 \times 10^9/L$ , hemoglobin of 10.9 g/dL and platelet count of  $149 \times 10^9/L$ . His absolute neutrophil count was markedly reduced at  $0.1 \times 10^9/L$ . Blast fraction was at 15%. Basophil fraction was elevated at 7%. A peripheral blood smear demonstrated pancytopenia [2.6K/cumm] with circulating blasts approximating 15% and rare Auer rods. Macrocytic anemia was noted with a granulocytic

dysplasia.

Reticulocyte production index was reduced at 0.3. APTT was 29.9 seconds with PT/INR of 13.1 seconds/1.02. Thrombin time of 14.8 seconds. D-dimer fraction was elevated at 300 ng/mL. Type and screen showed that he was O+. His chemistry was unremarkable with sodium of 141 mmol/L, potassium of 4.4 mmol/L, bicarbonate of 26 mmol/L, and creatinine of 1.19 mg/dL. TSH was 1.84 mIU/L, and serum albumin was 4.7 g/dL.

The clinical suspicion was for acute myeloid leukemia and the patient underwent bone marrow biopsy which revealed increased cellularity at 70 to 80% overall with a blast fraction comprising 40 to 50% of the marrow cellularity on CD34 immunostain. Dysplastic megakaryocytes were noted. The leukemic infiltrate was also positive for immunohistochemical stains for CD34, CD56 and myeloperoxidase. Flow cytometric analysis demonstrated acute myeloid leukemia with a CD45 dim+ blast population present amounting to 50% of total mononuclear cells with the following immunophenotype:

CD45dim+/CD13+/CD33+/CD34+

/CD38+/CD56+/CD117+/HLADR+/MPO+/TdT-

The background dysplasia suggested AML with MDS related changes and next generation sequencing, conventional cytogenetic studies, FLT3 mutation studies and fluorescent in situ hybridization [FISH] for MDS related changes, t[8; 21] and inv(16)/t(16;16) were ordered for final classification, which subsequently revealed loss of one copy of chromosome 7 as the sole anomaly in all metaphase cells analyzed.

In light of cytogenetic findings, CPX-351 liposome [Vyxeos] induction chemotherapy was initiated intravenously at 100unit/m<sup>2</sup> on days 1, 3 and 5 at approximately 90 minutes/infusion. Packed red blood cell transfusions and platelet concentrates were administered to maintain a hemoglobin goal of greater than 7 g/dL and platelet goal of greater than  $10 \times 10^9/L$  in the absence of active bleeding. Despite a decreasing transfusional requirement and marked symptomatic improvement, he still continued to require blood and platelet product transfusions, and the patient's clinical course was complicated a month later by an admission for gum bleeding which settled with topical tranexamic acid application.

Repeat bone marrow biopsy on day 28 showed marked reduction in myeloid blast fraction down

to 25%. Flow cytometry showed a reduction in CD34 positive myeloid blast fraction down to 11 to 12%. The patient subsequently underwent second cycle of induction chemotherapy with Vyxeos. Evaluation for allogeneic hematopoietic stem cell transplantation was concurrently underway. A third bone marrow biopsy done 2 weeks later showed further reduction in blast fraction down to about 5 to 8%. He is currently scheduled to undergo allogeneic hematopoietic stem cell transplantation.

### **Discussion:**

With regards to induction therapy for the management of acute myeloid leukemia for medically fit patients, current recommendations are to proceed with remission induction therapy with a 7-day continuous infusion of cytarabine at 100 mg/m<sup>2</sup> plus intravenous daunorubicin at 60 mg/m<sup>2</sup> on days 1, 2 and 3, the so-called 7+3 regimen. However, secondary AML, such as our patient with prior myelodysplastic syndrome is generally associated with an inferior prognosis and may require distinctive management. CPX-351 [Vyxeos] is a liposomal formulation of cytarabine and daunorubicin, and has been shown to achieve superior median overall survival and overall remission compared to 7+3 across all age groups and AML subtypes for the management of therapy-related myeloid neoplasms<sup>[4]</sup>. Studies have also demonstrated superior survival outcomes in older AML populations, a population traditionally considered to be high risk<sup>[5]</sup>.

The karyotype of the leukemic cell is the strongest prognostic factor for response to induction therapy and survival in AML, and several cytogenetic risk classification systems exist that reflect this, such as the Southwest Oncology Group [SWOG], the Medical Research Council [MRC], and Cancer and Leukemia Group B [CALGB]<sup>[6-8]</sup>. While they vary slightly, three groups of patients may be distinguished in all of these: favorable, intermediate, and unfavorable cytogenetics, with monosomies of non sex chromosomes such as monosomy 7 having a dismal prognosis if treated with conventional chemotherapeutic strategies<sup>[9]</sup>. Vyxeos has been FDA approved for the treatment of newly diagnosed therapy-related acute myeloid leukemia [t-AML] or AML with myelodysplasia related changes in adults in pediatric patients 1 year old. A point of interest regarding this formulation is the synergistic 1:5 molar ratio of

daunorubicin and cytarabine, which has been shown to enhance the killing of leukemic cells in vitro and murine models<sup>[10]</sup>.

There is some experimental evidence that CXP-351 [Vyxeos] exhibits selective uptake in leukemic cells as compared to normal bone marrow cells in murine models<sup>[11]</sup>, which may help explain the discrepancy in outcomes between those treated with traditional 7+3 regimens and CXP-351 [Vyxeos]. Studies also show CXP-351 [Vyxeos] has a longer half-life in the plasma and bone marrow compared to traditional chemotherapy<sup>[12]</sup>, which may translate to a comparatively extended period of drug exposure, and an improved therapeutic effect. The impressive reduction in this patient's blast fraction following induction chemotherapy may be explained by the aforementioned mechanisms of action.

Monosomy of chromosome 7 is the most frequent autosomal monosomy in acute myeloid leukemia, constituting about 10% of sporadic adult MDS<sup>[13]</sup>. There are several syndromic predispositions to the development of monosomy 7 MDS/AML including but not limited to telomere disorders, DNA repair gene mutations as well as prior chemotherapy and acquired bone marrow failure. However, monosomy 7 MDS/AML that arises without evidence of germline genetic predisposition and in the absence of other predisposing medical conditions or treatments is considered sporadic, which our patient demonstrated, and this remains a rare phenomenon, accounting for perhaps no more than 5% of AML cases<sup>[14]</sup>.

### **Conclusion:**

This case demonstrates that CPX-351 liposome [Vyxeos] may be equally effective, if not superior, to existing induction chemotherapeutic protocols for the management of AML with unfavorable risk cytogenetics such as monosomy 7, which has traditionally been considered a poor prognostic factor. Although existing data provide evidence for the superiority of Vyxeos in achieving improved overall survival and remission rates in specific AML populations deemed to be high risk, further studies will be needed to properly elucidate the durability and the extent of the response to CPX-351 liposome [Vyxeos] induction chemotherapy as compared to existing induction chemotherapy regimens such as 7+3 in

specific AML populations with unfavorable risk cytogenetics such as monosomy 7.

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### **Consent**

Written informed consent was obtained from the patient.

### **Conflict of interest**

There are no conflicts of interest to report.

### **Author's contributions**

The authors meet the ICMJE authorship criteria. Jonathan Alejandro Vargas, Mohamed Aimal Ahmed-Khan and Teena Thomas managed the patient and collected the data. Jeltsina Sofia Sosa wrote the manuscript. Mohamed Zakee Mohamed Jiffry supervised and approved the final version of the work to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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### **Abbreviations**

AML – acute myeloid leukemia  
MDS – myelodysplastic syndrome  
FISH – Fluorescent in situ hybridization  
WBC – white blood cell count  
CD – Cluster of differentiation  
CBC – complete blood count  
APTT – activated partial thromboplastin time  
PT/INR – prothrombin time/international normalized ratio  
TSH – thyroid stimulating hormone  
dim - diindolylmethane  
HLADR – human leukocyte antigen DR isotype  
MPO – myeloperoxidase  
TdT – terminal deoxynucleotidyltransferase  
FLT3 - Fms Related Receptor Tyrosine Kinase 3  
SWOG - Southwest Oncology Group  
MRC - Medical Research Council  
CALGB - Cancer and Leukemia Group B  
t-AML - therapy-related acute myeloid leukemia

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