Midostaurin combined with CPX-351 (Vyxeos) appears safe for induction in FLT3 mutated acute myeloid leukemia

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Abboud R, Augustin M K, Walter J M, et al Midostaurin Combined With CPX-351 (Vyxeos) Appears Safe For Induction in FLT3 Mutated Acute Myeloid Leukemia. J Blood Disord Treat.2020;4(4):6-7.

ABSTRACT

AThis case series adds six cases to the recently distributed three cases portraying results in patients with AML getting acceptance with CPX-351 and midostaurin. This early clinical experience recommends beginning security of the blend, anyway some potential exceptional poison levels warrant further examination. One patient in this series endured cardiovascular breakdown, which is a known complexity of both CPX-351 and of midostaurin. It is hazy if the mix raises the rate of cardiotoxicity. In a stage I/II examination in which azacitadine was joined with midostaurin, the frequency of diminished launch portion was 11%. Besides, one patient in our series experienced respiratory disappointment, potentially because of medication incited pneumonitis. Bronchoscopy and chest CT couldn't be performed because of clinical precariousness, and the conclusion couldn't be affirmed. Medication incited pneumonitis from midostaurin happens in up to 2% of patients and can be dealt with high portion corticosteroids8. The blend seems protected, yet certain chemotherapy and TKI related incidental effects ought to be checked methodicallly to guarantee the mix doesn't unduly raise the frequency or seriousness of these poison levels.

CASE REPORT INTRODUCTION

Acute Myeloid Leukemia (AML) is a clonal hematologic malignancy with widely varying prognosis based on cytogenetic and molecular features of an individual's disease [1,2]. After a long period without new effective therapies, there has been a relative explosion of new approved therapies for AML. In 2017 and 2018 alone, eight agents were approved and safe, effective combinations have yet to be elucidated. Two of these new agents are CPX-351 – a novel form of traditional cytarabine and daunorubicin - and midostaurin – a nonspecific Flt3 targeting small molecule inhibitor [3,4]. A subset of patients with newly diagnosed AML are eligible for CPX-351 induction based on cytogenetics and also for midostaurin induction based on Flt3 mutational status. But there is no randomized data showing the safety or effectiveness of the combination of these agents. Preclinical evidence suggests that multiple FLT3 inhibitors may have synergistic anti-leukemic activity when combined with CPX-351 [5]. AML cell lines containing FLT3-activating mutations are more sensitive to CPX-351, exhibiting increased drug uptake. However, the timing of administration may modify outcomes; pretreatment with FLT3 inhibitors has been shown to reduce the drug uptake of CPX-351 and leads to decreased AML cell death, whereas concurrent treatment leads to augmented apoptosis when compared with single-agent treatment [5]. A recent case series included three patients with AML treated with the combination on CPX-351 and midostaurin for first induction [6]. All three tolerated the combination well without additional myelosuppression or unexpected toxicities. All three achieved CR, although two were MRD positive by flow cytometry.

We performed a retrospective review of all patients who received CPX-351 and midostaurin for newly diagnosed AML harboring FLT3-ITD or –TKD mutations. We identified six patients who met criteria for inclusion between March 2018 and June 2019. We retrospectively reviewed charts for toxicities, and herein describe their outcomes. All patients were treated outside the context of a clinical trial. Patient characteristics and clinical course is summarized. Five patients had FLT3-ITD mutations and one had a FLT3-TKD mutation. Two patients received midostaurin with induction and consolidation, three with induction only, and one with consolidation only. Four patients are alive with median follow up of 200 days (range 131-403). Two patients underwent allogenic hematopoietic cell transplantation. All patients had neutrophil count recovery (median 34 days, range 28-39) and platelet count recovery (median 29 days, range 22-51) within expected time periods.

Two patients treated with CPX-351 and midostaurin have died. The first had relapsed disease during cycle two of consolidation and died during re-induction with cytarabine, cladribine, and G-CSF (CLAG) chemotherapy. The second died of respiratory failure 47 days after starting induction. The clinical differential diagnosis included drug induced pneumonitis, multifocal pneumonia, and diffuse alveolar hemorrhage. One patient was diagnosed with TKI induced heart failure after induction with CPX-351 and midostaurin, and no further TKI therapy was given.

This case series adds six cases to the previously published three cases describing outcomes in patients with AML receiving induction with CPX-351 and midostaurin. This early clinical experience suggests initial safety of the combination, however some potential unique toxicities warrant further investigation. One patient in this series suffered heart failure, which is a known complication of both CPX-351 and of midostaurin. It is unclear if the combination raises the incidence of cardiotoxicity. In a phase I/II study in which azacitadine was combined with midostaurin, the incidence of reduced ejection fraction was 11% [7]. Furthermore, one patient in our series suffered from respiratory failure, possibly due to drug induced pneumonitis. Bronchoscopy and chest CT could not be performed due to clinical instability, and the diagnosis could not be confirmed. Drug-induced pneumonitis from midostaurin occurs in up to 2% of patients and can be managed with high dose corticosteroids [8]. The combination appears safe, but certain chemotherapy and TKI related side effects should be monitored systematically in order to ensure the combination does not unduly raise the incidence or severity of these toxicities.

CONCLUSION

In this series, 4/5 patients evaluable for response achieved a CR and 4/6 were alive at the time of analysis. Two proceeded to allogeneic hematopoietic cell transplantation, one in first remission and one after relapse of disease. Because both agents showed effectiveness in phase III randomized trials, it is tempting to assume that the combination of CPX-351 and midostaurin would be a more effective induction strategy than either agent alone in patients with treatment related AML or AML with myelodysplasia-related and FLT3-ITD or –TKD mutations. However, this remains unproven, and preclinical data suggests that there is potential for either synergism or antagonism when these drugs are combined, depending on the schedule they are given. Future combination strategies should consider the timing of dosing to optimize pharmacologic interactions.

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AUTHORS CONTRIBUTION

RA, KA and JW designed and performed research, analyzed data, and authored the manuscript. MW, and CNA performed research and critically reviewed the manuscript.

CONFLICT OF INTEREST DISCLOSURE

RA, KA, MW, CNA, and JS have nothing to disclose regarding this manuscript.

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