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General AML, FLT3

The effect of CPX-351 *ex vivo* cytotoxicity on *FLT3-ITD* AML blast cells

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CPX-351 is a nano-scale liposome formulation of cytarabine plus daunorubicin co-encapsulated at a molar ratio of 5:1.

Max J. Gordon from the Oregon Health & Sciences University, Portland, USA, and colleagues published in Leukemia Research, data from their study, which aimed to identify Acute Myeloid Leukemia (AML) patients that respond to CPX-351 cytotoxicity using *ex vivo* testing. The article was originally published ahead of print on 12th December 2016.

To gain an understanding of the potential anti-neoplastic effect of CPX-351, the authors investigated the *ex vivo* cytotoxicity of CPX-351 in leukemia blasts cells isolated from fifty-three AML patients.

The key results are:

- Primary AML leukemia blast cells were sensitive to CPX-351 ex vivo below the reported 72hr plasma drug levels; median IC50 = 0.466:0.223 μM
- Overall ex vivo response to CPX-351 for AML patients with intermediate 2 or adverse cytogenetic risk (n = 16) was not significantly different to that of intermediate 1 (n = 21) and favorable risk AML patients (n = 3)
- In patients (n = 35) who received 7 + 3 therapy after blast cell isolation, 24/35 patients achieved Complete Response (CR) and 11/35 exhibited Progressive Disease (PD)
- No significant difference was found in CPX-351 IC50 values in patients that achieved CR and PD, P = 0.17
- Leukemia blasts from FMS-like Tyrosine Receptor Kinase 3 (FLT3)-Internal Tandem Duplication (ITD) patients (n = 14) had significantly lower mean CPX-351 IC50 compared to FLT3-ITD negative patients (n = 28)
- Cell sensitivity to CPX-351 (IC50) correlated with CPX-351 uptake efficiency; correlation coefficient = 0.703
- Ex vivo activity of CPX-351 was active in a range of hematologic malignancies

In summary, FLT3 mutated AML patients had higher sensitivity to CPX-351 induced cytotoxicity thus indicating that CPX-351 exhibits a potent cytotoxicity in high-risk AML patients. Additionally, the sensitivity of cells to CPX-351 is related to the degree of intracellular uptake of CPX-351 liposomes and drug release.

The authors highlighted that ex vivo sensitivity of AML blasts to CPX351 correlates with the clinical efficacy observed in AML patients in previous clinical trials and thus suggests that ex vivo testing could be useful in identifying AML patients with specific mutations or phenotype that could benefit from the therapeutic effects of CPX-351.

Abstract

Purpose

Identify AML patients most likely to respond to CPX-351, a nano-scale liposome formulation containing cytarabine and daunorubicin co-encapsulated at a 5:1 molar ratio.

Methods

We examined the ex vivo cytotoxic activity of CPX-351 against leukemic cells isolated from 53 AML patients and an additional 127 samples including acute lymphoblastic leukemia, myelodysplastic syndrome/myeloproliferative neoplasms, or chronic lymphocytic leukemia/lymphoma. We assessed activity with respect to common molecular lesions and used flow cytometry to assess CPX-351 cellular uptake.

Results

AML specimen sensitivity to CPX-351 was similar across conventional risk groups. FLT3-ITD cases were five-fold more sensitive to CPX-351. CPX-351 was active across other indications with nearly all cases exhibiting IC50 values markedly lower than reported 72-h plasma drug concentration in patients receiving CPX-351. The range and distribution of CPX-351 IC50 values were comparable for AML, CLL, and ALL, whereas MDS/MPN cases were less sensitive. CPX-351 uptake analysis revealed a correlation between uptake of CPX-351 and cytotoxic potency.

Conclusions

Our findings are consistent with clinical data, in which CPX-351 activity is retained in high-risk AML patients. Ex vivo analysis of cytotoxic potency may provide a means to identify specific AML subsets, such as FLT3-ITD, that benefit most from CPX-351 and warrant additional clinical evaluation.

References

1. Gordon M.J. *et al*. CPX-351 exhibits potent and direct ex vivo cytotoxicity against AML blasts with enhanced efficacy for cells harboring the FLT3-ITD mutation. Leukemia Research. 2017 February; 53: 39–49. DOI: 10.1016/j.leukres.2016.12.002. Epub 2016 Dec 12.