

# CPX-351 Cytarabine:Daunorubicin-containing liposomes accumulate in the bone marrow of leukemic mice

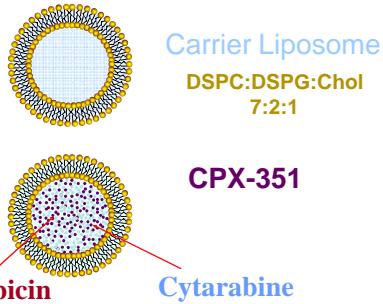
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Abstract 5534

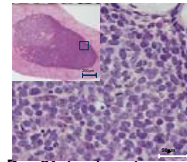


## Introduction

CPX-351 is a liposome formulation designed to deliver a synergistic, fixed ratio of cytarabine and daunorubicin in vivo. CPX-351 has been shown to be highly efficacious against a variety of mouse leukemia models, including the CCRF-CEM human T-lymphoblastoid leukemia xenograph (1). Encouraging results have also been obtained in early phase clinical trials. In this report we investigate liposome biodistribution properties that may contribute to the enhanced efficacy of CPX-351. We attributed the increased efficacy of CPX-351 over the free drug cocktail of cytarabine and daunorubicin to elevated exposure of the tumor tissue to chemotherapeutic agents.

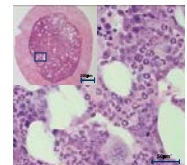


The CCRF-CEM tumor model efficiently engrafts to the bone marrow of SCID Rag2M mice inoculated with CCRF-CEM human T-lymphoblastoid leukemia



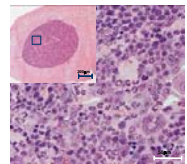
Day 21, treatment commences

21 days after tumor implantation, H&E stained bone marrow slices are consistent with lymphoproliferative disease (A).



Day 35, 14 days after treatment commenced

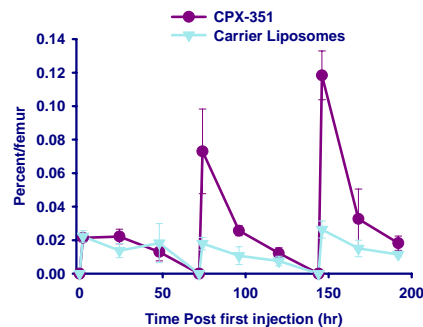
Treatment with CPX-351 induces regression of tumor-cells in bone marrow



Day 49, 28 days after treatment commenced

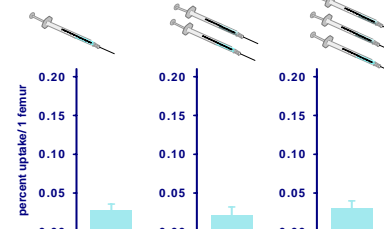
Subsequent to tumor regression, we observe normal bone marrow regeneration

Multiple injections of CPX-351 affected lipid accumulation in the bone marrow

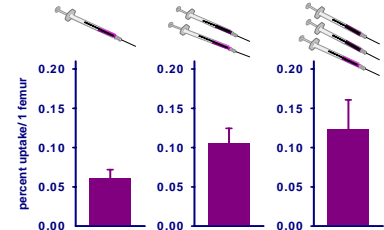


Tumor-bearing mice were injected with carrier liposomes, or CPX-351 Q3DX3 and bone marrow distribution was determined for each injection. Radioactively labelled lipid was injected only on the final injection. Bone marrow was collected 24 hours after injection radioactive lipid and the marker was quantified. Lipid dose 62 mg/kg. CPX-351 10 mg/kg cytarabine and 4.4 mg/kg daunorubicin

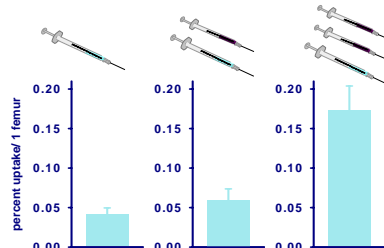
Bone marrow lipid accumulation was increased by the presence of cytarabine and daunorubicin in a previous dose



When leukemia-laden mice were injected with empty liposomes similar bone marrow accumulations were observed for each injection



When leukemia-laden mice were injected with CPX-351 liposomes the bone marrow accumulation was elevated relative to empty liposomes and lipid accumulation increased with each injection

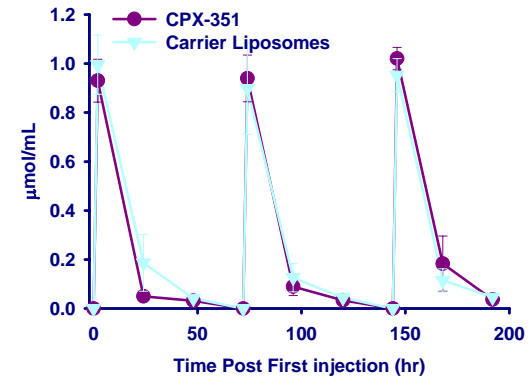


When leukemia-laden mice were exposed to CPX-351 prior to exposure to empty liposomes, the subsequent accumulation of empty liposomes increased

## Figure key



Plasma levels are comparable following administration of empty liposomes and CPX-351 for three injections



Tumor-bearing mice were injected with carrier liposomes, or CPX-351 on a Q3DX3 schedule and lipid circulation was followed for each injection. Radioactively labelled lipid was injected only on the final injection.

## Conclusions

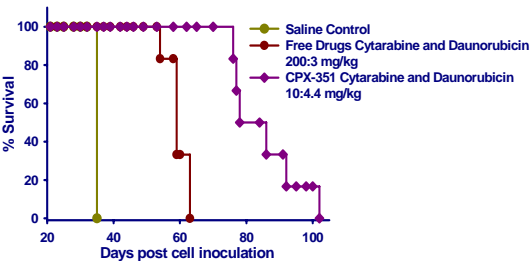
- Bone marrow uptake of CPX-351 liposomes is enhanced relative to carrier liposomes
- Administration of CPX-351 prior to carrier liposomes enhanced carrier liposome accumulation in bone marrow
- Increased bone marrow lipid accumulation of CPX-351 liposomes is not due to differences in circulation of the liposomes.
- Lipid accumulation is further increased with successive treatments of the leukemia suggesting that the liposomal drugs alter either the bone marrow microenvironment or resident cell populations in a manner that facilitates subsequent uptake and/or retention of CPX-351.

## Reference

Tardi P, Johnstone S, Harasym N, Xie S, Harasym T, Zisman N, Harvie P, Bermudes D, Mayer L. In vivo maintenance of synergistic cytarabine:daunorubicin ratios greatly enhances therapeutic efficacy. (2009) Leuk Res. 33(1):129-39.

## Methods and Results

CPX-351 is more effective than free drugs at prolonging the survival of mice bearing CCRF-CEM tumors



Rag2M mice were inoculated i.v. with CCRF-CEM human T-lymphoblastoid leukemia on day 0. Q3DX3 treatment commenced on day 21. Untreated mice succumbed ~35 days after tumor inoculation. CPX-351 prolonged the survival of tumor-bearing mice.