Pivarubicin is more effective than doxorubicin against triple-negative breast cancer in vivo

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Research article

Keywords: Pivarubicin, Doxorubicin, Apoptosis, Triple-Negative Breast Cancer, Chemotherapy, Cardiotoxicity

Posted Date: August 29th, 2019

DOI: <https://doi.org/10.21203/rs.2.13608/v1>

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Version of Record: A version of this preprint was published at Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics on December 10th, 2020. See the published version at <https://doi.org/10.3727/096504020X15898794315356>.

Abstract

Background: Triple-negative breast cancer (TNBC) is unresponsive to anti-estrogen and anti-HER2 therapies, requiring the use of cytotoxic drug combinations of anthracyclines, taxanes, cyclophosphamide and platinum compounds. Multidrug therapies achieve pathological cure rates of only 20-40%, a consequence of drug resistance and cumulative dose limitations necessitated by the irreversible cardiotoxic effects of anthracyclines and other cytotoxic agents. Safer and more effective treatments for TNBC are required to achieve durable therapeutic responses. This study describes the mechanism of action and in vivo efficacy of pivarubicin, a structurally and functionally novel anthracycline, to determine whether pivarubicin is potentially more effective and safer than doxorubicin against human primary TNBC. **Methods:** Hydrolytic stability, mechanism and ability of pivarubicin to circumvent mechanisms of resistance are tested in multiple tumor lines through modulation of PKC-delta activity and assessment of drug cytotoxicity. Comparative in vivo efficacy is tested in an orthotopic NSG mouse model implanted with MDA-MB-231 human TNBC cells and treated with the maximum tolerated doses of pivarubicin and doxorubicin, followed by monitoring of tumor growth by digital caliper measurements and determination of endpoint tumor weight and volume. Endpoint cardiotoxicity is assessed histologically by identifying microvacuolization in ventricular cardiomyocytes. **Results:** The trimethylester moiety of pivarubicin confers hydrolytic stability relative to the closely related congener, AD 198, but retains the ability of other N-alkylbenzyladriamycin compounds to directly activate PKC-delta and trigger rapid mitochondrial-dependent apoptosis. The structure and function of pivarubicin permits circumvention of resistance conferred by overexpression of P-glycoprotein, Bcl-2, Bcl-X L and Bcr-Abl. Primary tumors treated with the multiple rounds of the maximum tolerated dose (MTD) of doxorubicin failed to inhibit tumor growth compared with vehicle-treated tumors. However, administration of a single MTD of pivarubicin produced significant inhibition of tumor growth and tumor regression relative to tumor volume prior to initiation of treatment. Histological analysis of hearts excised from drug- and vehicle-treated mice revealed that pivarubicin produced no evidence of myocardial damage at this therapeutic dose. **Conclusion:** These results support the development of pivarubicin as a safer and more effective replacement for doxorubicin against TNBC as well as other malignancies for which doxorubicin therapy is indicated.

Full Text

The authors have retracted the full text of this preprint until journal publication