STRONG CHILDREN'S RESEARCH CENTER

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ABSTRACT

Title: *Daunorubicin shows promise as an alternative to doxorubicin with reduced overall late effects and cardiac health impacts in the treatment of Hodgkin lymphoma*

Background: Anthracyclines are old drugs (developed and clinically tested through the 1950s and 60s) used widely for treating various cancers as DNA intercalating agents. No safe dose of anthracyclines exists. The associated risk tends to increase with drug dose in a linear proportion, especially for chronic heart side effects. On average, the cited threshold for recommended cumulative lifetime dose for many anthracyclines is <250 mg/m^2. The anthracycline doxorubicin was introduced into Hodgkin lymphoma (HL) treatment regimens with success in the mid-1970s and therefore has not changed in years. New data (2015-2023) suggests that the doxorubicin precursor drug daunorubicin is less toxic than doxorubicin, in terms of late effects. It may be time to change the standard of care and allow patients to still be cured and live healthier.

Methods: A systematic literature review was conducted to compile available data on daunorubicin and doxorubicin application. Few direct comparison articles were found, so aggregate results were normalized relative to each other to obtain general ranges/representative values showing how the drugs differ. Articles for review were selected to allow for a wide range of analyses, including patients of all ages and outcomes, animal and cell studies, and review papers. The three aims for this investigation were to 1.) compare the relative cardiac late effects of doxorubicin and daunorubicin to determine if daunorubicin has substantially less impacts on the heart, 2.) analyze the pharmacokinetics of doxorubicin and daunorubicin to investigate their tissue distribution and plasma clearance over time, and 3.) assess the efficacy of daunorubicin in treating HL.

Results:

- Aim 1: Daunorubicin shows ~45-50% less adjusted risk of developing cardiac toxicity/chronic heart failure (HF) than doxorubicin. Also, both drugs show similar binding affinity to DNA and cardiolipin in mitochondrial membranes, which are abundant in cardiac myocytes, explaining the cardiac risk.
- Aim 2: Both drugs show similar, rapid clearance in their free state. Liposomal doxorubicin clears slower than liposomal daunorubicin, with the latter showing an exponentially decaying plasma concentration over time. Tissue distributions of both drugs (whether free or liposomal) are also similar.
- Aim 3: No data to date exists for daunorubicin use in HL so non-Hodgkin lymphoma (NHL) data was used as a surrogate since NHL typically requires more intensive treatment than HL. Free daunorubicin studies are limited in NHL also. Liposomal daunorubicin has shown a positive response in patients with refractory or relapsed NHL.

Conclusion: Cardiac late effects are significantly lower for daunorubicin compared to doxorubicin, suggesting that a switch would be beneficial for long-term cardiac health. Clearance and physiological distribution of daunorubicin is similar enough to that of doxorubicin to suggest that general toxicity and uptake is not a cause for concern. Because daunorubicin shows promise in treating aggressive NHL, its application in HL is expected to be efficacious also. Overall, change is warranted to allow for cure in HL patients and keep cumulative anthracycline dose below 250 mg/m^2. Also, further basic sciences studies on daunorubicin are needed, with the goal of moving towards clinical trials to assess the true efficacy of daunorubicin and patient outcomes in Hodgkin lymphoma.