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MEETING ABSTRACT

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Doxorubicin nanoparticles conjugated with *N*-(2-hydroxypropyl) methacrylamide exhibit low cardiotoxicity in rats

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Background: The clinical use of the highly effective antineoplastic agent doxorubicin is limited by late and irreversible life-threatening cardiotoxicity. Recently engineered doxorubicin-conjugated nanoparticles improved therapeutic index and tolerability. The aim of this study was to investigate cardiotoxicity induced by doxorubicin nanoparticles conjugated with *N*-(2-hydroxypropyl)methacrylamide.

Methods: Twenty-two male Wistar rats equipped with a radiotelemetric device (TA11PA-C40) were randomized into four experimental groups: Group 1 (HPMA; $n = 5$) was treated with *N*-(2-hydroxypropyl) methacrylamide (5 mg/kg; i.v.); group 2 (saline; $n = 5$) was treated with 0.9% NaCl (0.5 ml; i.v.); group 3 (HPMA-DOX; $n = 5$) was treated with *N*-(2-hydroxypropyl)methacrylamide conjugated with doxorubicin (5 mg/kg; i.v.), and group 4 (DOX; $n = 7$) was treated with doxorubicin (5 mg/kg, i.v.). Body weight (BW), blood pressure (BP), heart rate (HR), HR short-term variability (HRV), left ventricular ejection fraction (EF_{LV}) and left ventricular end-diastolic volume (EDV) were monitored for 140 days. Kaplan-Meier survial curves were calculated for all groups. At the end of the experiment, rats were euthanized and the harvested hearts were used for pathohistology.

Results: In the HPMA and saline groups, BW of rats increased over time and median survival was 140 days. BP, HR and HRV were comparable in both groups. However, EDV was increased in 3 HPMA-treated rats in respect to saline-treated rats. There were no pathohistological signs of cardiotoxicity in either the HPMA or saline group of rats. In HPMA-DOX rats BW increased over time and median survival was 140 days. BP, HR and HRV of these rats were comparable to controls while EDV was increased and EF_{LV} was decreased in 3 rats. Pathohistology revealed fibrosis in 3 rats. DOX rats exhibited a significant decline in BW and low median survival (16 days). In all DOX rats BP and HR were normal while EDV was increased and EF_{LV} and HRV were decreased. Pathohistological examination uncovered typical signs of cardiotoxicity in all DOX rats including severe fibrosis, vacuolization, necrosis and inflitration.

Discussion: Our results indicate that HPMA-DOX-treated rats have a better survival and lower cardiotoxicity than DOX-treated rats. These findings are in agreement with previous reports on doxorubicin survival in rats. EDV is the earliest indicator of heart failure in conventional echocardiography. Increase in EDV and decrease of EF_{LV} indicate left ventricular dilatation associated with heart failure in all rats treated with doxorubicin but only in 3 rats treated with HPMA-DOX. The increase of EDV in HPMA rats may reflect the increase of circulating volume due to the plasma-expander properties of HPMA as there was no pathohistological confirmation of cardiotoxicity in this group of rats. HRV was depressed only in DOX rats, which is an expected finding since reduction of HRV has been reported to predict poor survival in clinical settings.

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