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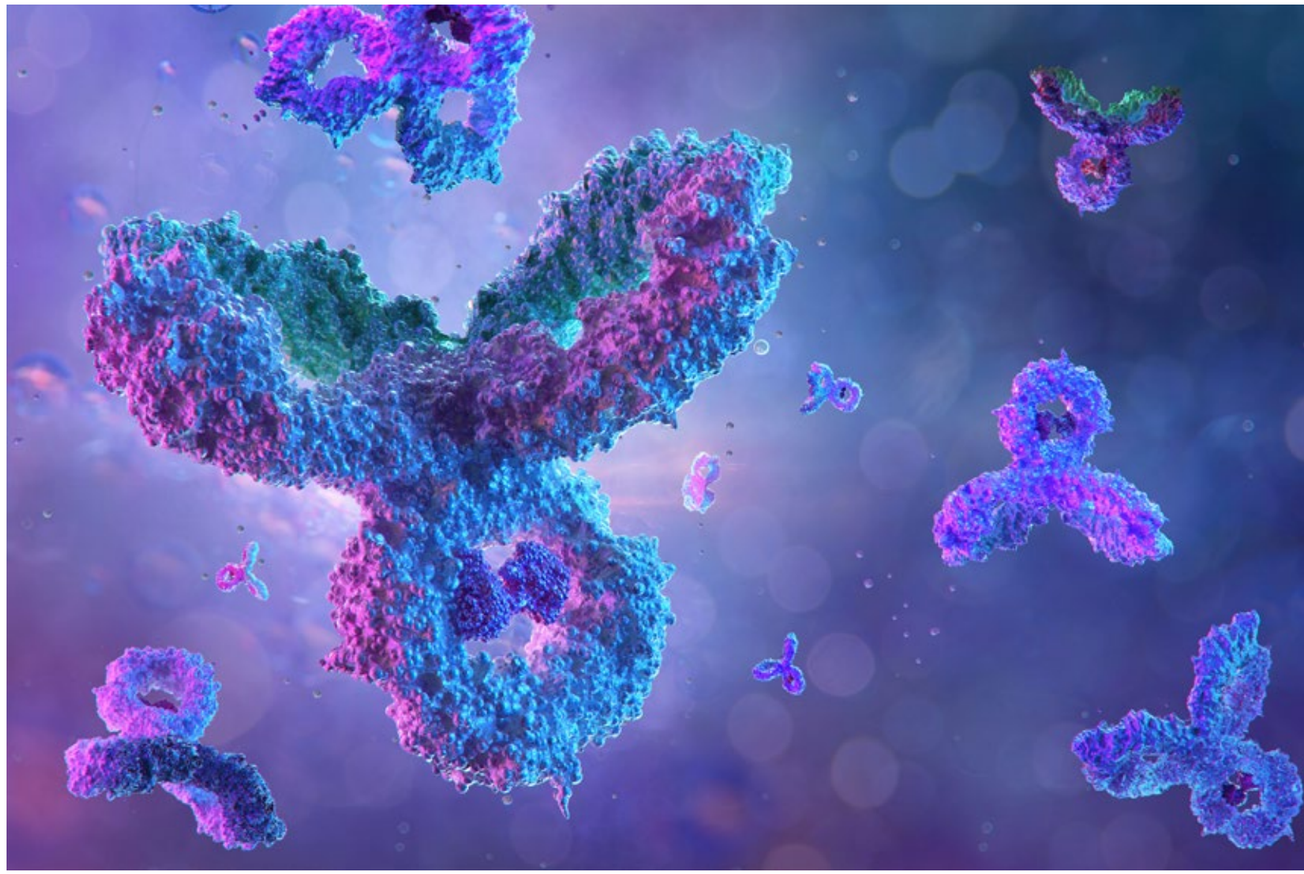

Summary of Three Toxicity Study of Repeated Intravenous Infusion of Exatecan Derivative-ADCs to Cynomolgus Monkey

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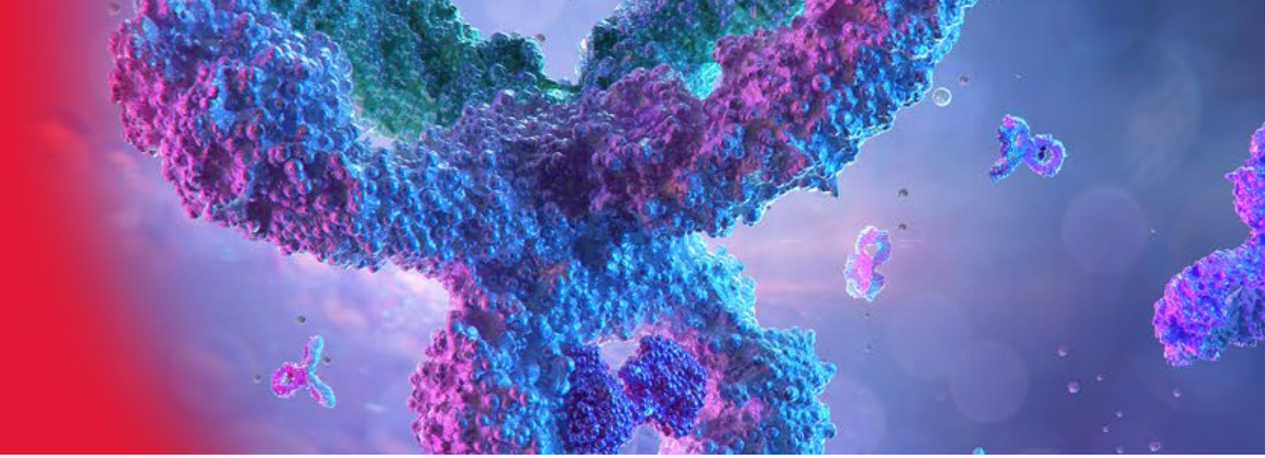

BACKGROUND & OBJECTIVE

Test articles A, B and C were three ADCs containing different targets of exatecan. This study summarizes the toxic reactions after repeated intravenous infusion of three exatecan ADCs of A, B and C, in cynomolgus monkeys conducted at JOINN Laboratories, providing toxicity reference data for the development of similar drugs.

METHODS

A total of 40 cynomolgus monkeys (20 animals/sex) were used and divided into 4 groups (5 animals/sex/group) and treated with vehicle control article and low-, middle-, and high-dose group in each study. The dosages of the test article A were 10, 30 and 45 mg/kg. The administration doses of test article B were 7.5, 15 and 30 & 20 mg/kg (30 mg/kg for the first administration and 20 mg/kg for the second and third administrations). The dosages of the test article C were 10, 30 and 50 mg/kg. All animals were administrated by intravenous infusion once every 3 weeks for a total of 2 or 3 times. During the study, clinical signs, body weight, clinical pathology, immune-related indicators, and histopathological examination were performed.The highest non-severely toxic dose (HNSTD) was 45 mg/kg for test article A, 15 mg/kg for test article B, and 50 mg/kg for test article C.

RESULTS

4/10 animals were found dead after dosing of 30 mg/kg test article B, and the cause of death was mainly related to malnutrition secondary to persistent diarrhea and deterioration of general condition. Neither mortality nor moribundity was noted in test article A and C. Transient loose stools were observed in all three test articles after administration. By comparing the exposure levels of exatecan, it was found that the systemic exposure of test article B was significantly higher than that of the test articles A and C, resulting in a relatively lower tolerated dose of test article B. The DAR values of in the test article A, B and C were 4, 8 and 8. The differences in the linker and the target led to the variations in the system exposure of the exatecan in each study, while no obvious relationship with the DAR values. Therefore, the tolerated dose of animals was positively correlated with the exposure to exatecan. The main toxicity of the three compounds was manifested as bone marrow hematopoietic system and immunosuppression, which was reflected in decreased red blood cell-related indicators (RBC, HGB, HCT, Retic), decreased number of lymphocytes in the medulla/cortex of the thymic cortex, decreased number of erythroid, erythroid granulocytes, hematopoietic cells in the bone marrow of the sternum and femur, and decreased number of lymphocytes in the germinal center of the spleen and the germinal center of the mesenteric, inguinal, mandibular lymph nodes. The toxicity of test article B was also noted in digestive system, skin and urinary system, including intestinal mucosal necrosis, hemorrhage, fibrin exudation, neutrophil infiltration, villous atrophy, intestinal lamina propria edema, villous epithelial detachment skin inflammation, ulceration, necrosis; renal tubular protein/cell casts and dilatation and tubular vacuolation. The systemic exposure of total antibody, ADC, and exatecan increased with the increase of dose, but there was no accumulation. No ADAs (antidrug antibodies) was detected in test article B, while obvious ADAs were observed in both test articles A and C, while no obvious impact on the exposure. There were no significant dose-related abnormal changes of food consumption, electrocardiogram, blood pressure, respiration, ophthalmoscopic examination, urinalysis, immune cell phenotype, immunoglobulin, complements, organ weight and macroscopic in each study.

Table 1 Correlation Data Between Systemic Exposure Level and Tolerated Dose

Test Article	DAR Value	HNSTD (mg/kg)	AUC of Exatecan at HNSTD (h*ng/mL)
A	4	45	318
B	8	15	125
C	8	50	466

RESULTS

In the literature, rapidly proliferative tissues, including hematopoietic (neutropenia, thrombocytopenia, anemia, lymphopenia), gastrointestinal (vomiting diarrhea), lymph nodes, and reproductive tissues, have been most prone to the toxic effects of exatecan. Noncumulative myelosuppression, particularly neutropenia, was the principal dose-limiting effect of exatecan in both rodents and dogs. These toxic reactions were also observed when using exatecan alone in monkeys. Compared with administration of exatecan alone, the hematological toxicity of exatecan containing ADCs, especially neutropenia, was significantly reduced after administration, and no toxicity of reproductive tissues was detected.

CONCLUSION

The tolerated dose of exatecan derivative ADCs given to cynomolgus monkeys was related to the systemic exposure to exatecan after administration. The administration of exatecan containing ADCs significantly reduced hematological toxicity. The main toxicities were bone marrow hematopoietic inhibition and immunosuppression.

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