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Cytidine Potentiates the Inhibitory Effect of Brequinar Sodium on Concordant Cardiac Xenograft Rejection

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RECENTLY brequinar sodium (BQR), has been described as a new immunosuppressive drug that inhibits de novo pyrimidine biosynthesis. By inhibiting the enzyme dihydroorotate dehydrogenase, BQR abrogates both DNA and RNA synthesis during cell proliferation. In addition, we have recently reported that BQR may also inhibit the activity of cytidine deaminase, which results in the potentiation of BQR's antilymphocytic activity when used in combination with cytidine, but not uridine.² BQR has been shown to be an effective immunosuppressive drug in preventing rejection of heart, liver, and kidney allografts and concordant cardiac xenograft in rats. However, in contrast to results reported by Cramer et al, our unpublished results showed that the prolongation of cardiac xenograft survival by BQR in the hamster-to-rat model was approximately 4 days, despite the administration of the same dose of BQR. Based on the potentiation of BOR's antilymphocytic effect by cytidine in vitro, we attempted to confirm the stronger immunosuppressive effect of BQR plus cytidine in this cardiac xenograft model. In addition, the effect of administering BQR plus cytidine on the serum lymphocytotoxic antibody levels was measured.

As shown in Fig 1a, the mean graft survival time of hamster heart grafts was 3 days (n = 6) for the untreated controls. Cytidine, at a dose of 73 mg/kg per day, did not affect the mean graft survival time $(3.4 \pm 0.5 \text{ days}, n = 8)$.

In contrast, BQR, at a dose of 3 mg/kg per day, significantly prolonged hamster heart graft survival to 6.8 ± 1.3 days (n = 12, P < .005 compared with untreated controls). When combining BQR 3 mg/kg per day with cytidine 73 mg/kg per day, hamster heart graft survival was further prolonged to 21.4 ± 12.7 days (n = 14, P = .001 compared with BQR treated recipients). Among these 14 animals, 3 recipients died on days 23, 26, and 31 with functioning grafts. This result shows that the administration of BQR plus cytidine represents a more potent immunosuppressive protocol for control of cardiac xenograft rejection.

As shown in Fig 1b, treatment of cardiac xenograft recipients with BQR caused an approximately three-fold reduction in cytotoxic antibody level between days 5 and 7 after transplant. Combination of BQR and cytidine resulted in a further slight reduction in antibody titre, but antibody level increased gradually despite continuous treatment.

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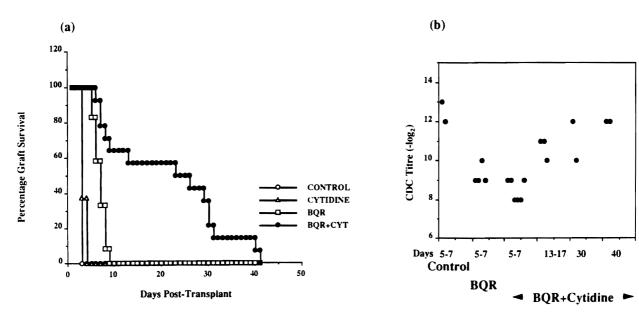


Fig 1. (A) Prolongation of cardiac xenograft survival by a combination of BQR and cytidine. (B) Antihamster cytotoxic antibody titres.

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