

DNA-dependent protein kinase overexpression is associated with poor prognosis B-CLL: a new therapeutic target

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Defects in DNA damage-inducible signalling pathways confer poor prognosis in chronic lymphocytic leukaemia (CLL). del(17p), del(11q), p53 dysfunction and mutations in ataxia telangiectasia-mutated kinase (ATM) predict chemoresistance and reduced survival. However, increased activity of the DNA repair enzyme, DNA-dependent protein kinase (DNA-PK), also correlates with chemoresistance. We explored the concept that increased DNA-PK function may be related to poor prognosis, using 60 CLL cases that had been characterised for cytogenetic abnormalities, CD38 and ZAP-70 expression.

DNA-PK catalytic subunit (cs) activity correlated with DNA-PKcs expression ($p = 0.001$; $n = 18$). DNA-PKcs expression varied 50-fold ($n = 31$), and was significantly higher ($p=0.01$) in del(17p) cases and consistently higher in del(11q) cases *versus* cases with del(13q) as the sole abnormality. DNA-PKcs was activated (autophosphorylation at ser2056) in intact CLL cells following *ex vivo* drug treatment, and activation was suppressed by the DNA-PK inhibitor, NU7441. NU7441 sensitised CLL cells to fludarabine, chlorambucil, 4-hydroperoxycyclophosphamide, etoposide and mitoxantrone (*ex vivo* viability assays) in samples from Binet stage A, B and C cases, including those harbouring del(17p), del(11q) and p53 mutation. Furthermore, γ H2AX foci and Comet assays showed that NU7441 increased drug-induced DNA double strand break levels, demonstrating that DNA-PK mediates repair in CLL.

Kaplan-Meier analysis indicated that cases with high DNA-PKcs expression showed a trend towards shorter treatment-free interval ($p=0.11$), pointing to a role for DNA-PK function in disease progression. These data merit confirmation with a larger cohort, and support the concept of targeting DNA-PK in poor-prognosis CLL.