ANTICANCER DRUGS

Mitotic arrest

DOI:
10.1038/nrd2317

One possible approach for cancer therapy is to develop inhibitors that block the function of key molecules that are required for complete cell division. Steegmaier and colleagues, writing in *Current Biology*, have identified an inhibitor of polo-like kinase 1 (PLK1) — a serine/threonine-specific kinase that is highly expressed in malignant cells — that inhibits tumour growth through the inhibition of mitosis.

By screening a compound library for the ability to inhibit the catalytic activity of PLK1, the authors identified BI 2536 as a potent (IC_{50} <1 nM) inhibitor, which showed more than 1,000-fold selectivity for PLK1 over a panel of 63 other kinases. The authors then examined the effect of BI 2536 on the cell-cycle profile of HeLa cancer cells *in vitro*. Application of the compound resulted in the absence of anaphase and telophase figures, accompanied by an accumulation of mitotic cells with aberrant spindles — the most prominent observed cellular phenotype was monopolar spindles. Remarkably, application of nanomolar concentrations of BI 2536 resulted in a phenotype similar to that observed with *PLK1* knockdown using RNAi. In synchronized HeLa cells, BI 2536 caused cells to undergo mitotic arrest, resulting in DNA breakdown and apoptosis. Moreover, BI 2536 potently inhibited the proliferation of 32 human cancer cell lines originating from diverse organ derivations such as breast, colon, lung, prostate, melanomas and haematopoietic cancers. These cells were also representative of varied patterns of tumour suppressor or oncogene mutations.

Next, the authors examined the ability of BI 2536 to block the growth of human cancer xenografts that were transplanted into immunodeficient mice. Consecutive cycles of intravenous injection of BI 2536 into mice with colon cancer xenografts resulted in a complete suppression of tumour growth. Furthermore, in a xenograft model of established colon cancer, repeated cycles of BI 2536 induced marked tumour regression. Similar findings were observed in models of pancreatic carcinoma and non-small-cell lung cancer. Good compound tolerability was observed during dosing regimes in all models.

With a view towards potential clinical evaluation, the authors investigated imaging methods suitable for *in vivo* monitoring of tumour regression. Using optical near infrared imaging of the murine lung-cancer model, a surge in apoptosis following initiation of BI 2536 treatment could be visualized, and using magnetic resonance imaging it was possible to identify structural changes in colon cancer tumours, which resulted from progressive apoptosis.

Collectively, these findings indicate that a PLK1 inhibitor could have efficacy against a range of human cancers. Indeed, BI 2536 has drug-like properties and has undergone Phase I clinical trials in patients with advanced local or metastatic cancers.

Charlotte Harrison

ORIGINAL RESEARCH PAPER Steegmaier, M. *et al.* BI 2536, a potent and selective inhibitor of polo-like kinase 1, inhibits tumour growth *in vivo*. *Curr. Biol.* **17**, 316–322 (2007)