Chapter 5b

Tales of how great drugs were brought down by a flawed rationale -- Letter

Michel D. Wissing, Michael A. Carducci, Hans Gelderblom, Paul J. van Diest

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Introduction

In January 2012, Komlodi-Pasztor and colleagues published a paper in which they explained why, in their opinion, the rationale used for these inhibitors was flawed.[1] They concluded there is a low likelihood that any inhibitor of mitotic enzymes would play a role in the management of solid tumors. In the letter to the editor presented below, we explain why their reasoning is incorrect, leading to a conclusion we consider preliminary.

Letter

In a recent article, Komlodi-Pasztor and colleagues argued that cancer researchers used a flawed rationale to develop inhibitors of mitotic enzymes, such as polo-like kinase 1 (PLK1) and aurora kinases.[1] Scientists had been misled by the success of microtubule-targeting agents (MTA) by assuming that MTAs act on cancer cells solely by mitotic inhibition, whereas their primary targets are microtubules in interphase. Inhibitors of enzymes solely expressed during mitosis would not have a significant antitumor effect on solid tumors in clinical studies, as most solid tumors have a mean mitotic index of less than 1%.

However, despite the low mitotic index, mitotic enzymes are frequently overexpressed in cancer; for example, Weichert and colleagues reported that 52.6% of all human prostate carcinomas have strong expression of PLK1.[2] This suggests that mitotic enzymes also play a role beyond mitosis. Indeed, PLK1 has been found to regulate among others p53 and microtubule dynamics in interphase as well.[3]

The authors describe that cancer cells have mitotic slippage after 1 to 2 days of treatment with antimitotic agents.[1] They fail to mention that such cells either become aneuploid or polyploid, or are arrested in interphase.[4] Although cells may initially be viable, all these states eventually result in cell death.

The authors explain the discrepancy between *in vivo* results and clinical efficacy of antimitotic agents further by the (twice) daily administration in mice, whereas in humans intravenous administration is done at a weekly or longer interval.[1] With the discovery of orally bioavailable compounds, such as the aurora kinase-inhibitors alisertib (MLN-8237), ENMD-2076, PF-03814735, MK-5108, and AMG-900 and the PLK1-inhibitors HMN-214, TAK-960, and NMS-1286937, similar dosing frequencies can be achieved in humans as in mice.

The major advantage of inhibitors of mitotic enzymes compared with MTAs is the lack of irreversible neuropathy after treatment; adverse events are fewer and rarely irreversible. Research is ongoing to increase the efficacy of aurora kinase- and PLK1-inhibitors, which could be accomplished by increased bioavailability to the tumor, that is, oral bioavailability, an improved pharmacokinetic profile, or activation by tumor-specific markers. Furthermore, addition of granulocyte colony-stimulating factor suppresses the adverse effect of mitotic inhibitors on the bone marrow, thereby allowing higher dosing. Aurora kinase- and PLK1-inhibitors could also have clinical potential in combination therapy, as combination therapy

could result in equal/improved efficacy and decreased toxicity compared with current treatment protocols. Therefore, we think that these promising agents should be further developed and deserve thorough testing in clinical trials.

References

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