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Not so WEE

Targeting G_2/M to kill mesothelioma cells

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It has been known for many years that manipulation of cell cycle checkpoint function represents one approach by which the toxicity of chemotherapy and of ionizing radiation can be increased in tumor cells.[1-3] In particular, abrogation of the G_2/M checkpoint has been shown to enhance the lethality of a wide range of toxic stresses.[1-3] Inhibition of the G_2/M checkpoint after chemotherapy/irradiation would result in tumor cells entering mitosis with damaged DNA, which would in turn result in loss of clonogenic survival (i.e., a lethal mitosis).

The mitotic cell cycle checkpoint is regulated by the kinase CDK1, which in turn is regulated by both ATM/ATR-CHK1/2-CDC25C signaling and by the tyrosine kinase WEE1.[4,5] Hence after DNA damage, inhibitors of WEE1 can be deployed and act to block phosphorylation of CDK1, thereby promoting CDK1 activity and inappropriate cell cycle progression. The WEE1 inhibitor MK-1775 has entered phase I clinical trials combined with gemcitabine, cisplatin or carboplatin in solid tumor patients.[6] The studies by Indovina et al. determined whether MK-1775 sensitized malignant mesothelioma cells to a standard of care therapeutic agent for this malignancy, cisplatin.[7]

In cells that lack a functional G_1/S arrest mechanism, DNA damage-induced G_2/M arrest represents the major cell cycle response. In this regard, MK-1775 has been shown to specifically enhance 5-fluorouracil toxicity in colon cancer cells lacking p53/a G_1/S arrest.[8] The actions of MK-1775 also correlate with impaired DNA repair.[9] It has also been shown that WEE1 inhibition forces S phase arrested cells directly into mitosis without completing DNA synthesis, which results in tumor cell death.[10]

In the present studies, in a dose-dependent and synergistic fashion MK-1775 enhanced cisplatin toxicity in 5 out of 6 mesothelioma cell lines but did not kill non-transformed fibroblasts. These findings with MK-1775 correlated with reduced numbers of stalled cells in G_2/M phase of the cell cycle after cisplatin treatment. Studies then determined whether cells that were permitted to enter mitosis harbored DNA damage the authors examined histone phosphorylation. It was found that MK-1775 forced mesothelioma cells to enter mitosis regardless of the presence of DNA damage, which is likely associated with enhanced killing when MK-1775 was combined with cisplatin. As judged using annexin–PI apoptosis assays cell killing was largely apoptotic, and that was associated with enhanced caspase 3 activity.

The present studies did not determine whether the in vitro combination effects of MK-1775 and cisplatin translate into an animal model of mesothelioma, though of note MK-1775 has been shown to enhance cisplatin toxicity in vivo in an ovarian cancer model.[11] As mesothelioma generally has such a poor outcome/survivorship, it will be of interest to see whether this drug combination approach will be tested in the clinic.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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