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In vitro treatment of mesothelioma with cell cycle inhibition and pemetrexed

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Introduction: Mesothelioma therapy is a highly fatal disease with limited therapeutic options. Pemetrexed forms the backbone of first line chemotherapy in mesothelioma. The major mechanism of action of pemetrexed is thought to be via inhibition of the folic acid synthesis pathway via inhibition of thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase. Low expression of the endogenous CDK4/CDK6 inhibitor and tumor suppressor p16INK4A has been demonstrated in up to 50-90% of mesothelioma tumors.Inhibition of CDK4 has been shown to be associated with decreased levels of thymidylate synthase and cell cycle arrest at the G1/S transition. Decreased levels of thymidylate synthase have been associated with increased response to pemetrexed in some studies.

Hypothesis: Palbociclib will sensitizemesothelioma cells to pemetrexed-based therapy.

Results: Previously, we have demonstrated that palbociclib inhibits mesothelioma cell proliferation, inhibits retinoblastoma protein phosphorylation, and results in cell cycle arrest. Mesothelioma cells in culture were treated with palbociclib and pemetrexed alone and in combination. At concentrations at 100 μM or greater, single agent palbociclib was associated with decreased cell proliferation versus single agent pemetrexed. At higher concentrations of palbociclib and pemetrexed (> 100 nM), no additive or synergistic effects were observed for the combination therapy against mesothelioma cell lines. Preliminary results are consistent with at least an additive effect on cell proliferation in H2373 and H2461 mesothelioma cells at 1 μM palbociclib plus 10 nM pemetrexed. In H2373 cells treatment with palbociclib at 10 μM results in complete inhibition of phosphorylation of site T826 in Rb, while treatment with 1 μM palbociclib results in partial inhibition of phosphorylation at the same site. Treatment with 100 nM pemetrexed plus 1 μM palbociclib resulted in complete inhibition of phosphorylation at T826.

Conclusion: Pemetrexed affects Rb phosphorylation and may sensitize mesothelioma cells to treatment with CDK4/6 inhibitor palbociclib. Further investigation of this combination approach may be useful for mesothelioma treatment.

Biography:

Mark Klein, M.D. is an Assistant Professor of Medicine at the University of Minnesota and a staff physician at the Minneapolis VA Healthcare System. He earned his M.D. from the University of Iowa and did internal medicine residency and hematology/oncology fellowship training at the University of Minnesota. His laboratory research interests include identifying new treatment strategies against mesothelioma and small cell lung cancer and therapeutic peptide design and development.