WEE1 Inhibition Enhances the Radiation Response in DIPG

Caretti et al. ____________ Page 141

Diffuse intrinsic pontine glioma (DIPG) is a fatal pediatric disease. Thus far, no therapeutic agent has proven beneficial in the treatment of this brain malignancy. Caretti and colleagues investigated the potential radiation-enhancing effects of a clinically relevant WEE1 inhibitor, MK-1775, in vitro and in vivo DIPG model. They show that WEE1 is overexpressed in DIPG and that its inhibition in vitro and in vivo resulted in additional antitumor effects when combined with radiotherapy. These results show that inhibition of WEE1 kinase in conjunction with radiotherapy holds potential as a therapeutic approach for the treatment of DIPG.

Combination Differentiation Therapy of Bortezomib and ATRA

Ying et al. ____________ Page 195

Proteasome-dependent degradation of RAR leads to decreased AML cell differentiation efficiency. To further sensitize cells to retinoids and extend the range of retinoid-affected myeloid malignancies beyond APL, Ying and colleagues evaluated the interaction of bortezomib, the first Food and Drug Administration-approved proteasome inhibitor, with ATRA in AML cells. They observed that bortezomib sensitized AML cells to ATRA-induced myeloid differentiation in vivo and in vitro. These enhanced differentiation effects were accompanied by RAR stabilization and STAT1 activation. The study was the first to evaluate bortezomib/ATRA synergy in AML cell and to assess new opportunities for bortezomib/ATRA combination as a promising approach for future differentiation therapy.

EGFR Exon 20 Insertions in Lung Cancer

Arcila et al. ____________ Page 220

Insertions in exon 20 of EGFR are a highly heterogeneous family of activating mutations with an incidence that is notably higher than generally appreciated (11% of all EGFR mutations), making them the third most common EGFR mutation after exon 19 deletions and the L858R point mutation. Arcila and colleagues’ in silico molecular modeling studies show that the various insertions predict different effects on erlotinib binding. They conclude that the high structural variability of these mutations may confer diversity in biologic behavior and response to targeted therapies, arguing against the blanket designation of all insertions as “nonresponsive” to EGFR tyrosine kinase inhibitors. Given the high incidence of lung adenocarcinomas, they estimate that testing could identify over 5000 patients with these mutations every year in the United States alone. Preclinical research and drug development represent unmet needs in this underestimated subgroup of lung cancer patients.