2595 General Poster Session (Board #8A), Mon, 8:00 AM - 12:00 PM

Phase I trial of sequential azacitidine and valproic acid plus carboplatin in the treatment of patients with advanced malignancies.

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Background: The combination of DNA methylation inhibitors and histone deacetylase inhibitors is synergistic in gene expression activation and may overcome platinum resistance. We hypothesized that sequential treatment with azacitidine and valproic acid (VPA) in combination with carboplatin would overcome resistance to platinum-based therapy, and we performed a phase I trial to assess safety, MTD, and clinical correlates. **Methods:** Patients (pts) with advanced solid tumors refractory to standard therapy were eligible. Pts received azacitidine, VPA, and carboplatin on a 28-day cycle, with stair-step dose escalation. Pts received azacitidine for 5 days from day 1 to day 5, VPA for 7 days from days 5 to 11, and carboplatin on days 3 and 10. Clinical correlates included evaluation of epigenetic changes, methylation patterns, and histone acetylation levels in peripheral blood monocytes. **Results:** 32 pts were treated, and the MTD was identified as azacitidine 75 mg/m^2 VPA 20 mg/kg, and carboplatin AUC 3.0. Minor responses or stable disease lasting $\geq$ 4 months was achieved by 6 pts (18.8%), including 3 pts with ovarian (9, 7, and 5 months), 1 pt with cervical (5 months), 1 pt with prostate (11 months), and 1 pt with colorectal cancer (5 months). Three out of the 10 pts with platinum-resistant or platinum-refractory ovarian cancer had SD for more than 4 months, and four had at least a 30% reduction in CA-125 level (82%, 47%, 38%, and 36%). 78% of pts developed grade 3 or 4 toxicities. DLTs occurred in 6 pts, including 4 pts with G3 altered mental status; 1 pt with G4 neutropenia, G3 fever, G3 anemia; and 1 pt with G4 neutropenia. Overall, the most common toxicities were fatigue 78%, neutropenia 63%, anemia 47%, nausea 44%, and thrombocytopenia 41%. **Conclusions:** Combination of azacitidine, VPA and carboplatin demonstrates preliminary evidence of antitumor activity in advanced malignancies. Six (18.8%) patients achieved minor responses or prolonged stable disease lasting $\geq$ 4 months. 78% of the patients developed grade 3 or 4 toxicities. Ongoing clinical correlates of epigenetic changes, methylation patterns, and histone acetylation levels will be presented.