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Meeting abstract

A phase II study of epigenetic therapy with hydralazine and magnesium valproate to overcome chemotherapy resistance in refractory solid tumors

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Background

Chemotherapy resistance, either innate or acquired requires for its development, expression changes on a large number of genes therefore, it has been hypothesized that epigenetic-mediated changes could be the driving force for chemotherapy resistance. Aberrant DNA methylation and histone deacetylation are the main epigenetic alterations in cancer, hence we hypothesized that hydralazine, a DNA methylation inhibitor and valproate, a histone deacetylase inhibitor may overcome resistance in refractory solid tumors.

Methodology

This is a MinExpSize 2-stage phase II open-label, single-arm study in which patients with advanced solid tumors who were progressing at the second or third cycle of first, second, third, fourth or fifth line of palliative chemotherapy were included. Patients were typed for acetylator phenotype and then treated with hydralazine at a daily dose of 182 mg for rapid or 83 mg for slow-acetylators, and magnesium valproate at 40 mg/kg. Both drugs were started at day -7 and continued until chemotherapy ended. Chemotherapy consisted of the same pre-study protocol regimen on which patients progressed. Response and toxicity were evaluated.

Main findings

From a total of 27 patients that signed informed consent, 17 patients were evaluable for toxicity and 15 patients for response. The primary sites in the 15 evaluable patients were cervix (3), breast (3), lung (1), testis (1) and ovarian (7) carcinomas. A clinical benefit (complete response, partial response or disease stabilization) was observed in 12 (80%) patients, 4 partial responses and 8 stable disease. The treatment was well tolerated even though the studied population was heavily pretreated. The most significant toxicity was hematological. Grade 3 and 4 toxicities were anemia, neutropenia, leukopenia and thrombocytopenia in 23.5%, 41.1%, 47% and 35.2% respectively. The main non-hematological toxicity was drowsiness, mostly grade 2. The median survival was 6 months.

Conclusion

Hydralazine and magnesium valproate are able to overcome chemotherapy resistance in a heavily treated patient population. The obtaining of partial responses and disease stabilization regardless of the tumor type and chemotherapy schedule strongly supports the concept that epigenetic agents can erase the epigenetic mark associated with the chemoresistant phenotype of cancer cells. These results are in line with our observations in breast and cervical cancer patients that hydralazine and valproate can up-regulate a huge number of tumor suppressor genes. Thus, epigenetic therapy with hydralazine and valproate can be added to the armamentarium for cancer therapy.