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Meeting abstract

A proof-of-principle study of epigenetic therapy with hydralazine and magnesium valproate plus doxorubicin cyclophosphamide as neoadjuvant therapy for locally advanced breast cancer

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Background

Aberrant DNA methylation and histone deacetylation participate in cancer development and progression, hence their reversal by inhibitors of DNA methylation and histone deacetylases (HDACs) is undergoing clinical testing in cancer therapy. As epigenetic alterations are common to breast cancer, in this proof-of-concept study, the demethylating hydralazine plus the HDACs inhibitor magnesium valproate were added to neoadjuvant doxorubicin and cyclophosphamide in locally advanced breast cancer to assess their safety and biological efficacy.

Materials and methods

Patients were typed for acetylator phenotype and then treated with hydralazine at 182 mg for rapid or 83 mg for slow-acetylators, and magnesium valproate at 30 mg/Kg, starting from day -7 until chemotherapy ended which consisted in four cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2, every 21 days. Core needle biopsies were taken from the primary breast tumors at diagnosis and at day 8 of treatment with hydralazine and valproate.

Results

Sixteen patients were included and received treatment as planed. All were evaluated for clinical response and toxicity and 15 for pathological response. Treatment was well-tolerated. The most common toxicity was drowsiness grades 1–2. Five (31%) patients had clinical CR and eight (50%) PR for an ORR of 81%. No one progressed. One out of 15 operated patients (6.6%) had pathological CR and 70% had residual disease <3 cm. There was a statistically significant decrease in global 5^{m}C content and HDAC activity. Hydralazine and magnesium valproate up and down-regulated at least 3-fold, 1091 and 89 genes respectively. Among up-regulated genes there were several tumor suppressor genes including p53.

Conclusion

Hydralazine and magnesium valproate produce DNA demethylation, HDAC inhibition and gene reactivation in the primary tumors. This treatment associated with doxorubicin and cyclophosphamide is safe, well-tolerated and seems to increase the efficacy of chemotherapy. A randomized phase III study is ongoing to support the efficacy of the so called epigenetic or transcriptional cancer therapy.